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=> d stat que

L1             1 SEA FILE=REGISTRY "IL 11"/CN
L2            15 SEA FILE=REGISTRY INTERLEUKIN 11?/CN
L3             5 SEA FILE=REGISTRY ("INTERLEUKIN 11 RECEPTOR (HUMAN CLONE 17.1
                  GENE IL11RA .ALPHA.-CHAIN PRECURSOR)"/CN OR "INTERLEUKIN 11
                  RECEPTOR (HUMAN CLONE HCR1 PRECURSOR)"/CN OR "INTERLEUKIN 11
                  RECEPTOR (HUMAN CLONE HCR2 ISOFORM PRECURSOR C-TERMINAL
                  FRAGMENT)"/CN OR "INTERLEUKIN 11 RECEPTOR (HUMAN GENE IL11RA
                  .ALPHA.-CHAIN PRECURSOR)"/CN OR "INTERLEUKIN 11 RECEPTOR
                  (MOUSE GENE IL11R.ALPHA.)"/CN OR "INTERLEUKIN 11 RECEPTOR
                  (MOUSE GENE IL11R.BETA.)"/CN OR "INTERLEUKIN 11 RECEPTOR
                  (MOUSE STRAIN CD-1 GENE IL11RA2 .ALPHA.-CHAIN PRECURSOR
                  REDUCED)"/CN)
L4            10 SEA FILE=REGISTRY L2 NOT L3
L5             2 SEA FILE=REGISTRY ("GP130 (CHICKEN)"/CN OR "GP130 (HUMAN)"/CN)

L6             1 SEA FILE=REGISTRY "GP 130"/CN
L7             1 SEA FILE=REGISTRY "GLYCOPROTEIN 130 (HUMAN HEPG2 CELL)"/CN
L8          1014 SEA FILE=HCAPLUS L1 OR L4 OR (IL OR INTERLEUKIN)(W)11
L10          100 SEA FILE=HCAPLUS L3 OR (IL OR INTERLEUKIN)(W)(11R OR 11(W)(R
                  OR RECEPTOR?))
L11         1167 SEA FILE=HCAPLUS L5 OR L6 OR L7 OR GP130 OR GP(W)130
L12           42 SEA FILE=HCAPLUS L8 AND L10 AND L11
L14           12 SEA FILE=HCAPLUS L12 AND (?OSTEO? OR ?OSTEOPOROS? OR BONE? OR
                  BONY)
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=> d ibib abs hitrn l14 1-12

L14 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:414689 HCAPLUS
DOCUMENT NUMBER: 134:70094
TITLE: **Interleukin-11** enhancement of VLA-5 mediated adhesion of CD34+ cells from cord blood to fibronectin is associated with the PI-3 kinase pathway
AUTHOR(S): Wang, Li-Sheng; Liu, Hong-Jun; Broxmeyer, Hal. E.; Lu, Li
CORPORATE SOURCE: The Department of Microbiology/Immunology, The Walther Oncology Center, Indiana University School of Medicine, Indianapolis, IN, 46202-5254, USA
SOURCE: In Vivo (2000), 14(2), 331-337
CODEN: IVIVE4; ISSN: 0258-851X
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Adhesion is required for cell growth, differentiation, survival, and function. Cell adhesion is mediated by a structurally diverse group of plasma membrane receptors, each exhibiting specialized ligand-binding properties that are needed for specific tasks. Intergrin-mediated adhesion is important for hematopoietic stem (HSC)/progenitor (HPC) cell survival and may prevent programmed cell death. Interleukin (**IL**)-**11**, a multi-functional cytokine secreted by the **bone** marrow environment, plays an important role in regulating growth and differentiation of HSCs/HPCs. In this report, we demonstrate that IL-II enhanced adhesion of freshly isolated and 3 day-expanded CD34+ cells to immobilized fibronectin. The expression of very late antigen (VLA)-4 and VLA-5 integrins was detected on CD34+ cells. CD34+ cells also expressed a-chain and **gp 130** subunits of the **IL-11 receptor** (R). Enhanced adhesion by **IL-11** was mediated via activation of VLA-5 integrins, since this action could be blocked by monoclonal antibodies against .beta.1 and .alpha.5, but not .alpha.4, integrins. Addn. of phosphatidylinositol (PI)-3 kinase inhibitors blocked **IL-11** enhanced adhesion of CD34+ cells to fibronectin. The results suggest that this enhanced adhesion is assocd. with the PI-3 kinase pathway, an inside-out signaling pathway.
IT **42013-48-9, Gp130**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(**interleukin-11** enhancement of VLA-5 mediated adhesion of CD34+ cells from cord blood to fibronectin is assocd. with the PI-3 kinase pathway in relation to)
REFERENCE COUNT: 41
REFERENCE(S): (2) Becker, P; Exp Hematol 1999, V27, P533 HCAPLUS
(3) Chen, Q; J Biol Chem 1994, V269, P26602 HCAPLUS
(4) Clark, E; Science 1995, V268, P233 HCAPLUS
(6) Du, X; Blood 1994, V83, P2023 HCAPLUS
(7) Fuhrer, D; Biochem Biophys Res Commun 1996, V224, P289 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:55514 HCAPLUS
DOCUMENT NUMBER: 132:192209
TITLE: The residual megakaryocyte and platelet production in c-mpl-deficient mice is not dependent on the actions of interleukin-6, **interleukin-11**, or leukemia inhibitory factor
AUTHOR(S): Gainsford, Timothy; Nandurkar, Harshal; Metcalf, Donald; Robb, Lorraine; Begley, C. Glenn; Alexander, Warren S.
CORPORATE SOURCE: The Walter and Eliza Hall Institute for Medical Research, the Cooperative Research Centre for Cellular Growth Factors and the Rotary Bone Marrow Research Laboratories, Royal Melbourne Hospital, Victoria, 3050, Australia
SOURCE: Blood (2000), 95(2), 528-534
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mice lacking thrombopoietin (TPO) or its receptor c-Mpl are severely thrombocytopenic, consistent with a dominant physiol. role for this cytokine in megakaryocytopoiesis. However, these mice remain healthy and show no signs of spontaneous hemorrhage, implying that TPO-independent mechanisms for platelet prodn. exist and are sufficient for hemostasis. To investigate the roles of cytokines that act through the **gp130** signaling chain in the residual platelet prodn. of mpl-/- mice, mpl-/-IL-6-/-, mpl-/-LIF-/-, and mpl-/-**IL-11R**.alpha.-/- double-mutant mice were generated. In each of these compd. mutants, the no. of circulating platelets was no lower than that obsd. in mice lacking only the c-mpl gene. Moreover, the deficits in the nos. of megakaryocytes and megakaryocyte progenitor cells in the **bone** marrow and spleen were no further exacerbated in mpl-/-IL-6-/-, mpl-/-LIF-/-, or mpl-/-**IL-11R**.alpha.-/- double-mutant mice compared with those in Mpl-deficient animals. In single IL-6-/-, LIF-/-, and **IL-11R**.alpha.-/- mutant mice, platelet prodn. was normal. These data establish that, as single regulators, IL-6, **IL-11**, and LIF have no essential role in normal steady-state megakaryocytopoiesis, and are not required for the residual megakaryocyte and platelet prodn. seen in the c-mpl-/- mouse.
REFERENCE COUNT: 40
REFERENCE(S): (1) Alexander, W; Blood 1996, V87, P2162 HCAPLUS
(2) Banu, N; Blood 1995, V86, P1331 HCAPLUS
(3) Basser, R; Lancet 1996, V348, P1279 HCAPLUS
(4) Bernad, A; Immunity 1994, V1, P725 HCAPLUS
(5) Betz, U; J Exp Med 1998, V188, P1955 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:753092 HCAPLUS
DOCUMENT NUMBER: 132:2795
TITLE: Antagonists of **interleukin 11**-mediated **osteoporotic bone** loss
INVENTOR(S): Shaughnessy, Stephen; Austin, Richard Carl
PATENT ASSIGNEE(S): Hamilton Civic Hospital Research Development

Corporation, Can.
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959608	A2	19991125	WO 1999-CA516	19990519
WO 9959608	A3	20000406		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9940277	A1	19991206	AU 1999-40277	19990519
PRIORITY APPLN. INFO.:			CA 1998-2237915	19980519
			WO 1999-CA516	19990519

AB The authors disclose that **interleukin-11** is a potent inhibitor of **bone** nodule formation, promotes **osteoclast** formation in **bone** marrow cultures, and mediates **bone** d. loss in a mouse **osteoporosis** model. In one example of **interleukin-11** antagonism, the authors disclose that sol. **IL-11 receptor** constructs, modified at the **gp130** binding site, ameliorate the **IL-11** -assocd. **bone** d. loss. In a second example, peptides derived from the ligand interaction site of **IL-11R** are also shown to reverse the pathol. **bone** loss.

L14 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:738815 HCAPLUS
DOCUMENT NUMBER: 132:48837
TITLE: Chimeric cytokine receptor can transduce expansion signals in interleukin 6 receptor .alpha. (IL-6R.alpha.)-, **IL-11R**.alpha.-, and **gp130**-low-to-negative primitive hematopoietic progenitors
AUTHOR(S): Takagi, Mineo; Nakamura, Takanori; Sawada, Toshie; Kaneko, Azusa; Nozaki-Ukai, Manabu; Nakahata, Tatsutoshi; Yokota, Takashi; Heike, Toshio
CORPORATE SOURCE: Department of Stem Cell Regulation, Institute of Medical Science, The University of Tokyo, Tokyo, 108-8639, Japan
SOURCE: Mol. Biol. Cell (1999), 10(11), 3633-3642
CODEN: MBCEEV; ISSN: 1059-1524
PUBLISHER: American Society for Cell Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors generated transgenic mice expressing chimeric receptors, which comprise extracellular domains of the human granulocyte-macrophage

colony-stimulating factor (hGM-CSF) receptor and transmembrane and cytoplasmic domains of the mouse leukemia inhibitory factor receptor. In suspension cultures of lineage-neg. (Lin-), 5-fluorouracil-resistant **bone** marrow cells of the transgenic mice, a combination of hGM-CSF and stem cell factor (SCF) induced exponential expansions of mixed colony-forming unit. The combination of hGM-CSF and SCF was effective on enriched, Lin-Sca-1+c-kit+ progenitors and increased either mixed colony-forming unit or cobblestone area-forming cells. In case of stimulation with hGM-CSF and SCF, interleukin-6 (IL-6) and SCF, or **IL-11** and SCF, the most efficient expansion was achieved with hGM-CSF and SCF. When Lin-Sca-1+c-kit+CD34- further enriched progenitors were clone sorted and individually incubated in the presence of SCF, hGM-CSF stimulated a larger no. of cells than did IL-6, IL-6 and sol. IL-6 receptor (IL-6R), or **IL-11**. These data suggest the presence of IL-6R.alpha.-, **IL-11R**.alpha.-, and **gp130**-low-to-neg. primitive hematopoietic progenitors. Such primitive progenitors are equipped with signal transduction mols. and can expand when these chimeric receptors are genetically introduced into the cells and stimulated with hGM-CSF in the presence of SCF.

REFERENCE COUNT: 28
REFERENCE(S):
(1) Deberry, C; Biochem J 1997, V327, P73 HCAPLUS
(2) Escary, J; Nature 1993, V363, P361 HCAPLUS
(3) Hirano, T; Int Rev Immunol 1998, V16, P249 HCAPLUS
(4) Hirota, H; J Exp Med 1996, V183, P2627 HCAPLUS
(6) Holyoake, T; Blood 1996, V87, P4589 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:243837 HCAPLUS
DOCUMENT NUMBER: 129:12368
TITLE: Suppression of **interleukin-11** -mediated **bone** resorption by cyclooxygenases inhibitors
AUTHOR(S): Morinaga, Yoshihiro; Fujita, Naoya; Ohishi, Kazuo; Zhang, Yongke; Tsuruo, Takashi
CORPORATE SOURCE: Institute of Molecular and Cellular Biosciences, University of Tokyo, Tokyo, Japan
SOURCE: J. Cell. Physiol. (1998), 175(3), 247-254
CODEN: JCLLAX; ISSN: 0021-9541
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We previously found that human melanoma (A375M) and human breast cancer (MDA-MB-231) cells formed **osteolytic bone** metastasis in vivo. These cancer cells produced **interleukin-11** (**IL-11**) by themselves and stimulated its prodn. from **osteoblasts**. **Interleukin-11** could increase the no. of **osteoclasts** and raise the calcium concn. in the medium of neonatal murine calvaria organ culture, indicating **bone** resorption in vitro. Therefore, **IL-11** could play an important role in the promotion of **osteolysis** at the site of **bone** metastasis. In the present study, we used the calvaria culture system to try to clarify the mechanisms of **IL-11** -mediated **bone** resorption. The murine calvaria expressed both the specificity-detg. a subunit and the signal-transducing .beta. subunit (**gp130**) of the **IL-11 receptor**.

When **IL-11** was added to the calvaria culture, the concns. of prostaglandin E2 (PGE2) was elevated. Pretreatment of calvaria with cyclooxygenases inhibitors (e.g., indomethacin, NS-398, and dexamethasone) suppressed the prodn. of PGE2 and the **bone** resorption induced by **IL-11**. Addn. of exogenous PGE2 overcame the inhibitory effect of cyclooxygenases inhibitors and promoted **bone** resorption. These results indicate that **IL-11** promotes **bone** resorption through a PGE2 synthesis-dependent mechanism and that cyclooxygenases inhibitors could be interesting drugs to suppress **IL-11**-mediated **osteolytic bone** metastasis of cancer cells.

L14 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:729867 HCAPLUS
DOCUMENT NUMBER: 128:21688
TITLE: Recombinant human **interleukin-11** directly promotes megakaryocytopoiesis in vitro
AUTHOR(S): Weich, Nadine S.; Wang, Anlai; Fitzgerald, Michael; Neben, Tamlyn Yee; Donaldson, Debra; Giannotti, Joann; Yetz-Aldape, Joanne; Leven, Robert M.; Turner, Katherine J.
CORPORATE SOURCE: Department of Immunology and Hematopoiesis, Genetics Institute, Inc, Cambridge, MA, 02140, USA
SOURCE: Blood (1997), 90(10), 3893-3902
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have investigated the mechanism of action of the thrombopoietic cytokine, recombinant human **interleukin-11** (rhIL-11), on megakaryocytopoiesis in vitro. We have shown that rhIL-11-induced murine and human megakaryocytopoiesis are not mediated by thrombopoietin (Tpo). Murine megakaryocytes (MKs) were produced from **bone** marrow (BM) mononuclear cells cultured with rhIL-11, IL-3, and a combination of the two cytokines. Conditioned media (CM) were collected and assayed for the presence of biol. active Tpo. Tpo activity was not detected in any of the CMs tested. Next, human BM CD34+ cells were cultured in serum-free fibrin clot medium with rhIL-11, IL-3, or rhIL-11 plus IL-3 and an antibody that neutralizes human Tpo activity. No inhibition of either burst-forming unit-MK- or colony-forming unit-MK-derived colony formation was obsd. The antibody did partially inhibit steel factor-induced MK-colony formation, suggesting that the actions of this cytokine are mediated, in part, by Tpo. We detd. that MKs can be direct targets of rhIL-11 by showing the expression of functional **IL-11 receptor** on these cells. Total RNA was prepd. from cultured human BM CD41+CD14- cells (MKs) and **IL-11 receptor** .alpha. chain mRNA was detected in the MKs by reverse transcription-polymerase chain reaction. Anal. of single sorted CD41+CD14- cells confirmed that the obsd. **IL-11 receptor** expression was not due to contaminating CD41- cells in the pool. The presence of rhIL-11 receptor .alpha. chain protein in the cells was established by Western blot anal. After a short exposure of purified BM MKs to rhIL-11, enhanced phosphorylation of both its signal transduction sub-unit, **gp130**, and the transcription factor, STAT3 was detected, showing a direct activation of receptor signaling by the cytokine. Consistent with the lack of effect of rhIL-11 on platelets

in vivo, **IL-11 receptor** .alpha. chain mRNA and protein were not detected in isolated human platelets. These data indicate that rhIL-11 acts directly on MKs and MK progenitors but not on platelets.

L14 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:607919 HCAPLUS
DOCUMENT NUMBER: 127:291888
TITLE: Adult mice with targeted mutation of the **interleukin-11 receptor** (IL11Ra) display normal hematopoiesis
AUTHOR(S): Nandurkar, Harshal H.; Robb, Lorraine; Tarlinton, David; Barnett, Louise; Kontgen, Frank; Begley, C. Glenn
CORPORATE SOURCE: The Walter and Eliza Hall Institute of Medical Research, The Cooperative Centre for Cellular Growth Factors, The Royal Melbourne Hospital, Victoria, 3050, Australia
SOURCE: Blood (1997), 90(6), 2148-2159
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Interleukin-11** (**IL-11**) is a pleiotropic growth factor with a prominent effect on megakaryopoiesis and thrombopoiesis. The receptor for **IL-11** is a heterodimer of the signal transduction unit **gp130** and a specific receptor component, the .alpha.-chain (**IL-11R**.alpha.). Two genes potentially encode the **IL-11R**.alpha.: the IL11Ra and IL11Ra2 gene. The IL11Ra gene is widely expressed in hematopoietic and other organs, whereas the IL11Ra2 gene is restricted to only some strains of mice and its expression is confined to testis, lymph node, and thymus. To investigate the essential actions mediated by the **IL-11R**.alpha., we have generated mice with a null mutation of IL11Ra (IL11Ra-/-) by gene targeting. Anal. of IL11Ra expression by Northern blot and reverse transcriptase-polymerase chain reaction, as well as the absence of response of IL11Ra-/- **bone** marrow cells to **IL-11** in hematopoietic assays, further confirmed the null mutation. Compensatory expression of the IL11Ra2 in **bone** marrow cells was not detected. IL11Ra-/- mice were healthy with normal nos. of peripheral blood white blood cells, hematocrit, and platelets. **Bone** marrow and spleen contained normal nos. of cells of all hematopoietic lineages, including megakaryocytes. Clonal cultures did not identify any perturbation of granulocyte-macrophage (GM), erythroid, or megakaryocyte progenitors. The no. of day-12 colony-forming unit-spleen progenitors were similar in wild-type and IL11Ra-/- mice. The kinetics of recovery of peripheral blood white blood cells, platelets, and **bone** marrow GM progenitors after treatment with 5-fluorouracil were the same in IL11Ra-/- and wild-type mice. Acute hemolytic stress was induced by phenylhydrazine and resulted in a 50% decrease in hematocrit. The recovery of hematocrit was comparable in IL11Ra-/- and wild-type mice. These observations indicate that **IL-11 receptor** signaling is dispensable for adult hematopoiesis.

L14 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:733105 HCAPLUS

DOCUMENT NUMBER: 126:17644
TITLE: Functional expression of soluble human **interleukin-11** (**IL-11**) **receptor** .alpha. and stoichiometry of in vitro **IL-11** **receptor** complexes with **gp130**
AUTHOR(S): Neddermann, Petra; Graziani, Rita; Ciliberto, Gennaro; Paonessa, Giacomo
CORPORATE SOURCE: Dep. Genetics, Inst. Ricerche Biol. Mol. "P. Angeletti" (IRBM), Pomezia (Roma), 00040, Italy
SOURCE: J. Biol. Chem. (1996), 271(48), 30986-30991
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The interleukin-6 (IL-6) family of cytokines activates signaling through the formation of either **gp130** homodimers, as for IL-6, or **gp130**-leukemia inhibitory factor receptor (LIFR) heterodimers as for ciliary neurotrophic factor (CNTF), leukemia inhibitory factor, oncostatinM, and cardiotrophin-1. Recent in vitro studies with IL-6 and CNTF have demonstrated that higher order hexameric receptor complexes are assembled in which signaling chain dimerization is accompanied by the dimerization of both the cytokine mol. and its specific receptor .alpha. subunits (IL-6R.alpha. or CNTFR.alpha., resp.). **IL-11** is a member of the IL-6 family and known to require **gp130** but not LIFR for signaling. In this study we investigate the functional and biochem. compn. of the **IL-11** **receptor** complex. The human **IL-11** **receptor** .alpha.-chain was cloned from a human **bone** marrow cDNA library. **IL-11R**.alpha. was shown to confer **IL-11** responsiveness to human hepatoma cells either by cDNA transfection or by adding a sol. form of the receptor (sIL11R.alpha.) expressed in the baculovirus system to the culture medium. In vitro immunopptn. expts. showed that sIL11R.alpha. specifically binds **IL-11** and that binding is enhanced by **gp130**. Similarly to IL-6 and CNTF, **gp130** is able to induce dimerization of the **IL-11**.cntdot.**IL-11R**.alpha. subcomplex, the result of which is the formation of a pentameric receptor complex. However, in contrast to the other two cytokines, **IL-11** was unable to induce either **gp130** homodimerization or **gp130**/LIFR heterodimerization. These results strongly suggest that an as yet unidentified receptor .beta.-chain is involved in **IL-11** signaling.

L14 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:372135 HCAPLUS
DOCUMENT NUMBER: 125:55871
TITLE: The role of **gp130**-mediated signals in **osteoclast** development: regulation of **interleukin 11** production by **osteoblasts** and distribution of its receptor in **bone** marrow cultures
AUTHOR(S): Romas, Evangelos; Udagawa, Nobuyuki; Zhou, Hong; Tamura, Tatsuya; Saito, Mikiyoshi; Taga, Tetsuya; Hilton, Douglas J.; Suda, Tatsuo; Ng, Kong Wah;

Martin, T. John
CORPORATE SOURCE: St. Vincent's Inst. Med. Res., Univ. Melbourne, Victoria, 3065, Australia
SOURCE: J. Exp. Med. (1996), 183(6), 2581-2591
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interleukin (**IL**)-**11** is a multifunctional cytokine whose role in **osteoclast** development has not been fully elucidated. The authors examd. **IL-11** prodn. by primary **osteoblasts** and the effects of rat monoclonal anti-mouse glycoprotein 130 (**gp130**) antibody on **osteoclast** formation, using a coculture of mouse **osteoblasts** and **bone** marrow cells. IL-1, TNF.alpha., PGE2, parathyroid hormone (PTH), and 1.alpha.,25-dihydroxyvitamin D3 (1.alpha.,25(OH)2D3) similarly induced prodn. of **IL-11** by **osteoblasts**, but IL-6, IL-4, and TGF.beta. did not. Primary **osteoblasts** constitutively expressed mRNAs for both **IL-11** **receptor** (**IL-11R**.alpha.) and **gp130**. **Osteotropic** factors did not modulate **IL-11R** .alpha. mRNA at 24 h, but steady-state **gp130** mRNA expression in **osteoblasts** was upregulated by 1.alpha.,25(OH)2D3, PTH, or IL-1. In cocultures, the formation of multinucleated **osteoclast**-like cells (OCLs) in response to **IL-11**, or IL-6 together with its sol. IL-6 receptor was dose-dependently inhibited by rat monoclonal anti-mouse **gp130** antibody. Furthermore, adding anti-**gp130** antibody abolished OCL formation induced by IL-1, and partially inhibited OCL formation induced by PGE2, PTH, or 1.alpha.,25(OH)2D3. During **osteoclast** formation in marrow cultures, a sequential relation existed between the expression of calcitonin receptor mRNA and **IL-11R**.alpha. mRNA. **Osteoblasts** as well as OCLs expressed transcripts for **IL** **-11R**.alpha., as indicated by RT-PCR anal. and in situ hybridization. These results suggest a central role of **gp130** -coupled cytokines, esp. **IL-11**, in **osteoclast** development. Since **osteoblasts** and mature **osteoclasts** expressed **IL-11R**.alpha. mRNA, both **bone** -forming and **bone**-resorbing cells are potential targets of **IL-11**.

L14 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:127596 HCAPLUS
DOCUMENT NUMBER: 124:173137
TITLE: Detection of receptors for interleukin-6, **interleukin-11**, leukemia inhibitory factor, oncostatin M, and ciliary neurotrophic factor in **bone** marrow stromal/**osteoblastic** cells
AUTHOR(S): Bellido, Teresita; Stahl, Neil; Farruggella, Thomas J.; Borba, Victoria; Yancopoulos, George D.; Manolagas, Stavros C.
CORPORATE SOURCE: Center for Osteoporosis and Metabolic Bone Diseases, University of Arkansas for Medical Sciences, Little Rock, AR, 72205, USA
SOURCE: J. Clin. Invest. (1996), 97(2), 431-7
CODEN: JCINAO; ISSN: 0021-9738

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The functional receptor complexes assembled in response to interleukin-6 and -11 (IL-6 and **IL-11**), leukemia inhibitory factor (LIF), oncostatin M (OSM), and ciliary neurotrophic factor (CNTF), all involve the signal transducer **gp130**: IL-6 and **IL-11** induce homodimerization of **gp130**, while the rest heterodimerize **gp130** with other **gp130**-related .beta. subunits. Some of these cytokines (IL-6, **IL-11**, and CNTF) also require a specificity-detg. .alpha. subunit not directly involved in signaling. The authors searched for functional receptor complexes for these cytokines in cells of the **bone** marrow stromal/**osteoblastic** lineage, using tyrosine phosphorylation of the .beta. subunits as a detection assay. Collectively, murine calvaria cells, **bone** marrow-derived murine cell lines (+/+LDA11 and MBA13.2), as well as murine (MC3T3-E1) and human (MG-63) **osteoblast**-like cell lines displayed all the previously recognized .alpha. and .beta. subunits of this family of receptors. However, individual cell types had different constellations of .alpha. and .beta. subunits. In addn. and in difference to the other cell types examd., MC3T3-E1 cells expressed a heretofore unrecognized form of **gp130** ; and MG-63 displayed an alternative form (type II) of the OSM receptor. Thus, stromal/**osteoblastic** cells are targets for the actions of all the members of the cytokine subfamily that shares the **gp130** signal transducer, and different receptor repertoires may be expressed at different stages of differentiation of this lineage.

L14 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:114524 HCAPLUS
DOCUMENT NUMBER: 124:199986
TITLE: The human **IL-11 receptor** requires **gp130** for signaling: demonstration by molecular cloning of the receptor
AUTHOR(S): Nandurkar, Harshal H.; Hilton, Douglas J.; Nathan, Paula; Willson, Tracy; Nicola, Nicos; Begley, C. Glenn
CORPORATE SOURCE: The Royal Melbourne Hospital, Victoria, 3050, Australia
SOURCE: Oncogene (1996), 12(3), 585-93
CODEN: ONCNES; ISSN: 0950-9232
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors describe the mol. cloning of a cDNA for the .alpha. chain of the human **IL-11 receptor** (**IL-11r**.alpha.) and demonstrate the requirement of either the human or mouse **gp130** mol. for signaling. The cDNA clones encoding **IL-11R**.alpha. were isolated from a **bone** marrow cDNA library using a fragment from the murine **IL-11R** .alpha. as a probe. The human receptor was predicted to consist of 422 amino acids and was found to share 84% identity with the murine protein. In the extracellular region it exhibited a single hemopoietin domain with conserved cysteine residues and WSTWS motif. The transmembrane region was followed by a short cytoplasmic tail which did not contain a tyrosine kinase domain. Interaction of the human **IL-11R**.alpha. with murine **gp130** was demonstrated: expression of the human **IL-11R**.alpha. in murine M1 cells which constitutively express murine **gp130** (and murine LIF receptor), resulted in the

generation of specific high-affinity binding sites for **IL-11** (Kd = 250 pM). In addn., expression of the human **IL-11R**.alpha. in these cells permitted the induction of macrophage differentiation in response to **IL-11**. These results suggested that the human **IL-11R**.alpha. chain was able to form a functional receptor complex in assocn. with murine **gp130**. The requirement of **gp130** for signaling was confirmed by expression of the human **IL-11R**.alpha. in Ba/F3 cells. Ba/F3 cells that expressed the human **IL-11R**.alpha. alone showed binding of radiolabeled **IL-11** but no proliferative response. Introduction of human **gp130** into these cells resulted in high-affinity **IL-11** binding sites and **IL-11** dependent cellular proliferation. Thus these results demonstrated the abs. requirement of **gp130** for signaling.

IT **174129-57-8**
RL: PRP (Properties)
(amino acid sequence; sequence of human **IL-11 receptor** .alpha.-chain cDNA and requirement of **gp130** for signaling in induction of macrophage differentiation and proliferation)

L14 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:827296 HCAPLUS
DOCUMENT NUMBER: 123:337025
TITLE: Molecular cloning of two isoforms of a receptor for the human hematopoietic cytokine **interleukin -11**
AUTHOR(S): Cherel, Michel; Sorel, Michel; Lebeau, Benoit; Dubois, Sigrid; Moreau, Jean-Francois; Bataille, Regis; Minvielle, Stephane; Jacques, Yannick
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Centre Hospitalier Universitaire, Fr.
SOURCE: Blood (1995), 86(7), 2534-40
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Interleukin-11** (**IL-11**) is a stromal cell-derived cytokine with multiple biol. activities on lymphohematopoietic cells. It belongs to a family of pleiotropic and redundant cytokines that use the **gp130** transducing subunit in their high affinity receptors. By amplifying human cDNA libraries with oligonucleotide primers corresponding to the conserved WSXWS motif found in the hematopoietic cytokine receptor family, a novel cytokine receptor cDNA was identified that, based on high (82%) sequence homol. with the recently cloned murine **IL-11 receptor**, appears to encode the human **IL-11 receptor**. This receptor is a 422-amino acid protein contg. a signal peptide followed by extracellular, transmembrane, and cytoplasmic domains. The extracellular region has a two-domain structure homologous to those of the IL-6 and ciliary neurotrophic factor (CNTF) receptors: an Ig-like domain and a cytokine receptor-like domain. In addn., an isoform of the human **IL-11 receptor** that lacks the cytoplasmic domain was also identified. In agreement with the pleiotropic effects of **IL-11** on different hematopoietic lineages and **bone** cells, **IL-11 receptor**

transcripts were expressed by the myelogenous leukemia cell line K5662, the megakaryocytic leukemia cell line Mo7E, the erythroleukemia cell line TF1, and the **osteosarcoma** cell lines MG-63 and Saos-2.

IT **168461-35-6 168461-36-7**
RL: PRP (Properties)
(amino acid sequence; mol. cloning of two isoforms of receptor for human hematopoietic cytokine **interleukin-11**)

=> d stat que l15

```
L1            1 SEA FILE=REGISTRY "IL 11"/CN
L2           15 SEA FILE=REGISTRY INTERLEUKIN 11?/CN
L3            5 SEA FILE=REGISTRY ("INTERLEUKIN 11 RECEPTOR (HUMAN CLONE 17.1
                GENE IL11RA .ALPHA.-CHAIN PRECURSOR)"/CN OR "INTERLEUKIN 11
                RECEPTOR (HUMAN CLONE HCR1 PRECURSOR)"/CN OR "INTERLEUKIN 11
                RECEPTOR (HUMAN CLONE HCR2 ISOFORM PRECURSOR C-TERMINAL
                FRAGMENT)"/CN OR "INTERLEUKIN 11 RECEPTOR (HUMAN GENE IL11RA
                .ALPHA.-CHAIN PRECURSOR)"/CN OR "INTERLEUKIN 11 RECEPTOR
                (MOUSE GENE IL11R.ALPHA.)"/CN OR "INTERLEUKIN 11 RECEPTOR
                (MOUSE GENE IL11R.BETA.)"/CN OR "INTERLEUKIN 11 RECEPTOR
                (MOUSE STRAIN CD-1 GENE IL11RA2 .ALPHA.-CHAIN PRECURSOR
                REDUCED)"/CN)
L4           10 SEA FILE=REGISTRY L2 NOT L3
L5            2 SEA FILE=REGISTRY ("GP130 (CHICKEN)"/CN OR "GP130 (HUMAN)"/CN)

L6            1 SEA FILE=REGISTRY "GP 130"/CN
L7            1 SEA FILE=REGISTRY "GLYCOPROTEIN 130 (HUMAN HEPG2 CELL)"/CN
L8         1014 SEA FILE=HCAPLUS L1 OR L4 OR (IL OR INTERLEUKIN)(W)11
L10         100 SEA FILE=HCAPLUS L3 OR (IL OR INTERLEUKIN)(W)(11R OR 11(W)(R
                OR RECEPTOR?))
L11        1167 SEA FILE=HCAPLUS L5 OR L6 OR L7 OR GP130 OR GP(W)130
L12          42 SEA FILE=HCAPLUS L8 AND L10 AND L11
L14          12 SEA FILE=HCAPLUS L12 AND (?OSTEO? OR ?OSTEOPOROS? OR BONE? OR
                BONY)
L15           4 SEA FILE=HCAPLUS (L12 AND (MUTAT? OR ALTER? OR CHANG?)) NOT
                L14
```

=> d ibib abs hitrn l15 1-4

L15 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:770354 HCAPLUS
TITLE: Expression of **interleukin-11** during the human menstrual cycle: Coincidence with stromal cell decidualization and relationship to leukaemia inhibitory factor and prolactin
AUTHOR(S): Dimitriadis, E.; Salamonsen, L. A.; Robb, L.
CORPORATE SOURCE: Prince Henry's Institute of Medical Research, Clayton, 3168, Australia
SOURCE: Mol. Hum. Reprod. (2000), 6(10), 907-914
CODEN: MHREFD; ISSN: 1360-9947
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Interleukin-11** (**IL-11**) is crucial in the decidualization response of the uterine stroma to the implanting blastocyst in the mouse. This study examd. the localization and expression of **IL-11** in human endometrium throughout the menstrual cycle and of prolactin and leukemia inhibitory factor (LIF) in secretory phase endometrium. The mRNA expression of **IL-11 receptor** .alpha. and the signalling component, **gp 130**, in endometrial tissue were also detd. Immunoreactive **IL-11** was highest in the secretory phase and present in decidualized stromal cells, glandular epithelial cells, endothelial and smooth muscle cells, and the mRNA expression was verified by in-situ hybridization. Decidual cells showed the most intense staining. **IL-11 receptor** .alpha. and **gp 130** mRNA were detected throughout the cycle with minimal variation. Expression of **IL-11** mRNA and protein preceded that of prolactin. While immunoreactive prolactin was found in stromal, decidual and glandular epithelial cells, prolactin mRNA was confined to decidual cells. In contrast, endometrial LIF expression preceded **IL-11** but was largely confined to the glandular epithelium. The sequence of appearance of LIF, **IL-11** and prolactin suggests a synchronized role for each in the differentiation of the endometrium. The cyclical **changes** and cell type specific expression of **IL-11** suggests a potential role in the decidualization of stromal cells.

REFERENCE COUNT: 30

REFERENCE(S):
(1) Bilinski, P; Genes Dev 1998, V12, P2234 HCAPLUS
(2) Braverman, M; J Clin Endocrinol Metab 1984, V58, P521 HCAPLUS
(3) Bryant-Greenwood, G; Mol Cell Endocrinol 1993, V95, P23 HCAPLUS
(4) Cullinan, E; Proc Natl Acad Sci USA 1996, V93, P3115 HCAPLUS
(5) Du, X; Blood 1994, V83, P2023 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:217949 HCAPLUS

DOCUMENT NUMBER: 133:3688

TITLE: **IL-11** activates human endothelial cells to resist immune-mediated injury

AUTHOR(S): Mahboubi, Keyvan; Biedermann, Barbara C.; Carroll, Joseph M.; Pober, Jordan S.

CORPORATE SOURCE: Molecular Cardiobiology Program, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, 06510, USA

SOURCE: J. Immunol. (2000), 164(7), 3837-3846
CODEN: JOIMA3; ISSN: 0022-1767

PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **IL-11**, a **gp130**-signaling cytokine, is protective in several in vivo models of immune-mediated and inflammatory injury. HUVECs express **IL-11 receptor** .alpha.-chain and **gp130**. Human **IL-11** causes rapid (2-10 min) tyrosine phosphorylation of **gp130**. **IL-11** at 0.1 and 10 ng/mL induces tyrosine phosphorylation of

STAT3 and STAT1, resp., although maximal responses require 50 ng/mL. Phospho-STAT3 and phospho-STAT1 levels peak rapidly (2.5 min) and disappear by 60 min. The p42 and p44 mitogen-activated protein kinases (MAPKs) are phosphorylated in response to 0.3 ng/mL **IL-11** with maximal activation at 30 ng/mL **IL-11**. Phosphorylation of p42 and p44 MAPKs, which can be prevented by a mitogen-activated protein/extracellular signal-related kinase kinase-1 inhibitor, peaks by 15-20 min and largely disappears by 40 min. **IL-11** does not activate NF-.kappa.B nor does it inhibit NF-.kappa.B activation by TNF. Similarly, **IL-11** neither induces E-selectin or ICAM-1 nor blocks induction by TNF. Although **IL-11** does not **alter** class I MHC complex mol. expression, pretreatment with 0.5 ng/mL **IL-11** partially protects HUVECs against lysis by allospecific class I MHC-restricted cytolytic T cells or by anti-class I MHC Ab plus heterologous C. **IL-11**-induced cytoprotection is protein synthesis-dependent and may depend on mitogen-activated protein/extracellular signal-related kinase kinase-1. Thus, low (i.e., STAT3- and MAPK-activating) concns. of **IL-11** confer resistance to immune-mediated injury in cultured HUVECs without inhibiting proinflammatory responses.

REFERENCE COUNT: 53

REFERENCE(S):
(1) Adunyah, S; Ann NY Acad Sci 1995, V766, P296 HCAPLUS
(2) Akira, S; Int J Biochem Cell Biol 1997, V29, P1401 HCAPLUS
(3) Auguste, P; J Biol Chem 1997, V272, P15760 HCAPLUS
(4) Biedermann, B; J Immunol 1998, V161, P4679 HCAPLUS
(5) Biedermann, B; J Immunol 1999, V162, P7022 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:335846 HCAPLUS

DOCUMENT NUMBER: 127:49045

TITLE: Interleukin-6 receptor antagonists inhibit **interleukin-11** biological activity

AUTHOR(S): Ren-Xiao, Sun; Gennaro, Ciliberto; Rocco, Savino; Zong-Jiang, Gu; Klein, Bernard

CORPORATE SOURCE: Unit Cellular Therapy, Hopital St. Eloi, Montpellier, 34000, Fr.

SOURCE: Eur. Cytokine Network (1997), 8(1), 51-56
CODEN: ECYNEJ; ISSN: 1148-5493

PUBLISHER: Libbey Eurotext

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The IL-6 receptor system comprises two functionally different chains: a binding chain (IL-6R) and a signal-transducing chain (**gp130**). The IL-6/IL-6R complexes assoc. with **gp130**, induce its dimerization and signal transduction. When IL-6 is completed to IL-6R, two distinct sites of IL-6 are able to bind **gp130**. Other cytokines - oncostatin M (OM), leukemia inhibitory factor (LIF) or ciliary neurotrophic factor (CNTF) also use the **gp130** transducer and induce its heterodimerization with LIF receptor (LIFR). A series of IL-6 mutants have been generated which function as IL-6 receptor antagonists (IL-6RA). These IL-6RA carried substitutions that increased their affinity with IL-6R and abolished 1 or the 2 sites of interaction with

gp130. All the IL-6RA inhibited wild-type IL-6. The IL-6RA with one **mutated** binding site to **gp130** inhibited **IL -11** activity. They did not affect those of CNTF, LIF and OM, even when used at a very high concn. at which virtually all membrane. IL-6R were bound to IL-6RA. IL-6RA with two **mutated** **gp130** binding sites did not affect **IL-11**, CNTF, LIF or OM activities. The results indicate that the interaction of one **gp130** chain with IL-6R/IL-6R complexes inhibited further the dimerization of **gp130** induced by **IL-11**/ **IL-11R** but not its heterodimerization with LIFR. Thus these IL-6RA can also function as **IL-11** antagonists.

L15 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:143458 HCAPLUS
DOCUMENT NUMBER: 126:223660
TITLE: Expression and function of members of the cytokine receptor superfamily on breast cancer cells
AUTHOR(S): Douglas, Andrea M.; Goss, Geraldine A.; Sutherland, Robert L.; Hilton, Douglas J.; Berndt, Michael C.; Nicola, Nicos A.; Begley, C. Glenn
CORPORATE SOURCE: Rotary Bone Marrow Research Laboratories, PO Royal Melbourne Hospital, Victoria, 3050, Australia
SOURCE: Oncogene (1997), 14(6), 661-669
CODEN: ONCNES; ISSN: 0950-9232
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Receptors for the cytokines leukemia inhibitory factor (LIF), interleukin-6 (IL-6), oncostatin M (OSM), ciliary neurotrophic factor (CNTF) and **interleukin-11** (**IL-11**) are members of the structurally conserved hemopoietin receptor superfamily. In addn., they all share the transmembrane signalling protein **gp130**. In this paper the expression and function of this family of receptors in breast cancer cells was examd. RT-PCR analyses demonstrated that **gp130** was expressed in 12/12 breast cell lines and the specific receptor .alpha.-chains for IL-6, LIF, **IL-11** and CNTF were expressed in the majority of these cell lines. This was in contrast to other hemopoietin receptors. Examn. of 50 clin. samples of malignant breast tissue by RT-PCR showed a similar pattern of expression of **gp130** assocd. receptors. Treatment of breast cancer cell lines with OSM resulted in **changes** in cellular morphol. Cellular proliferation was inhibited following exposure to OSM (3/4 cell lines), **IL-11** (2/4 cell lines), and by IL-6 and LIF (1/4 cell lines). Cell surface binding of LIF and OSM was also documented. The expression of these receptors in 12/12 cell lines and greater than 95% of clin. samples suggests that these mols. may be important in regulating the growth of breast cells.

=> d stat que

L18 17 SEA FILE=REGISTRY SILRPDPPQGLRVESVP|RRLXASW/SQSP
L19 11 SEA FILE=HCAPLUS L18

=> d ibib abs hitrn l19 1-11

L19 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:861800 HCAPLUS
DOCUMENT NUMBER: 134:28451
TITLE: Protein and cDNA sequences of human DNAX cytokine receptor subunit 2 (DCRS2)
INVENTOR(S): Dowling, Lynette M.; Timans, Jacqueline C.; Gorman, Daniel M.; Kastelein, Robert A.; Bazan, Fernando J.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000073451	A1	20001207	WO 2000-US14867	20000530

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-322913 19990601
AB The invention provides protein and cDNA sequences of human cytokine receptor proteins designated DNAX cytokine receptor subunit 2 (DCRS2). Antibodies, both polyclonal and monoclonal, are also provided. Methods of using the compns. for both diagnostic and therapeutic utilities are provided.
IT **168461-35-6 186004-58-0**
RL: PRP (Properties)
(unclaimed protein sequence; protein and cDNA sequences of human DNAX cytokine receptor subunit 2 (DCRS2))
REFERENCE COUNT: 3
REFERENCE(S): (1) Anon; DATABASE SWISSPROT 1995
(2) Elson, G; WO 9920755 A 1999 HCAPLUS
(3) Moore, K; US 5716804 A 1998 HCAPLUS

L19 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:753092 HCAPLUS
DOCUMENT NUMBER: 132:2795
TITLE: Antagonists of interleukin 11-mediated osteoporotic bone loss
INVENTOR(S): Shaughnessy, Stephen; Austin, Richard Carl
PATENT ASSIGNEE(S): Hamilton Civic Hospital Research Development Corporation, Can.
SOURCE: PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9959608	A2	19991125	WO 1999-CA516	19990519
WO 9959608	A3	20000406		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9940277	A1	19991206	AU 1999-40277	19990519
PRIORITY APPLN. INFO.:			CA 1998-2237915	19980519
			WO 1999-CA516	19990519

AB The authors disclose that interleukin-11 is a potent inhibitor of bone nodule formation, promotes osteoclast formation in bone marrow cultures, and mediates bone d. loss in a mouse osteoporosis model. In one example of interleukin-11 antagonism, the authors disclose that sol. IL-11 receptor constructs, modified at the gp130 binding site, ameliorate the IL-11-assocd. bone d. loss. In a second example, peptides derived from the ligand interaction site of IL-11R are also shown to reverse the pathol. bone loss.

IT **250688-37-0**, SILRPDPPQGLRVESVPGYP **250688-39-2**, SILRPDPPQGLRVESVPSYP
RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(interleukin-11-binding peptide antagonists of interleukin-11/IL-11 receptor/gp130 complex for treatment of pathol. bone loss)

IT **251306-39-5 251306-40-8 251306-41-9**
RL: PRP (Properties)
(unclaimed protein sequence; antagonists of interleukin 11-mediated osteoporotic bone loss)

L19 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	1997:198915 HCAPLUS
DOCUMENT NUMBER:	126:289609
TITLE:	Identification of a second murine interleukin-11 receptor .alpha.-chain gene (IL11Ra2) with a restricted pattern of expression
AUTHOR(S):	Robb, Lorraine; Hilton, Douglas J.; Brook-Carter, Phillip T.; Begley, C. Glenn
CORPORATE SOURCE:	Walter and Eliza Hall Inst. Medical Res., Royal Melbourne Hospital, Victoria, 3050, Australia
SOURCE:	Genomics (1997), 40(3), 387-394 CODEN: GNMCEP; ISSN: 0888-7543
PUBLISHER:	Academic
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB The interleukin-11 receptor .alpha.-chain, a member of the hematopoietin receptor superfamily, forms, together with gp130, a functional high-affinity receptor complex for interleukin 11. The authors, and others, reported the cloning of the murine interleukin 11 receptor

.alpha.-chain cDNA (IL11Ra) and recently described the structure of the IL11Ra locus. The authors also described the presence of a second IL11Ra-like locus in some mouse strains. In this study the authors report that the second locus, designated IL11Ra2, encodes an mRNA species. The transcript was 99% identical to the IL11Ra transcript in the coding and 3'-untranslated region, but had a different 5'-untranslated region. The complete genomic organization of the IL11Ra2 locus is presented, and the two loci are shown to be located on a 200-kb NaeI genomic fragment. Comparison of the expression pattern of the IL11Ra and IL11Ra2 genes using an RT-PCR restriction fragment length polymorphism strategy revealed that while the expression of IL11Ra was widespread, expression of IL11Ra2 was restricted to testis, lymph node, and thymus.

IT **186004-58-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; identification and sequence of murine interleukin-11 receptor .alpha.-chain gene IL11Ra2 with a restricted pattern of expression)

L19 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:2649 HCAPLUS
DOCUMENT NUMBER: 126:127547
TITLE: Two differentially expressed interleukin-11 receptor genes in the mouse genome
AUTHOR(S): Bilinski, Petra; Hall, Mark A.; Neuhaus, Herbert; Gissel, Cornelia; Heath, John K.; Gossler, Achim
CORPORATE SOURCE: The Jackson Laboratory, Bar Harbor, ME, 04609, USA
SOURCE: Biochem. J. (1996), 320(2), 359-363
CODEN: BIJOAK; ISSN: 0264-6021
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interleukin-11 (IL-11) is a multifunctional cytokine involved in the regulation of cell proliferation and differentiation in a variety of cell types and tissues in vitro and in vivo. The effects of IL-11 were shown to be mediated by the IL-11 receptor (hereafter referred to as IL-11R.alpha.), which is a ligand-binding subunit and provides ligand specificity in a functional multimeric signal-transduction complex with gp130. Here the authors show that the mouse genome contains a second gene encoding an IL-11-binding protein, referred to as IL-11R.beta.. The structure of the IL-11R.beta. gene is highly similar to that of IL-11R.alpha., and IL-11R.beta. exhibits 99% sequence identity with IL-11R.alpha. at the amino acid level. IL-11R.beta. is co-expressed with IL-11R.alpha., albeit at lower levels, in embryos and in various adult tissues. IL-11R.beta. transcripts are abundant in testis, and, in contrast with IL-11R.alpha., absent from skeletal muscle. IL-11R.beta. expressed in vitro binds IL-11 with high affinity, suggesting that the mouse genome contains a second functional IL-11R.

IT **186004-58-0**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(amino acid sequence; two differentially expressed interleukin-11 receptor genes in mouse genome)

IT **159994-99-7**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(amino acid sequence; two differentially expressed interleukin-11 receptor genes in mouse genome)

L19 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:464615 HCAPLUS
DOCUMENT NUMBER: 125:140563
TITLE: Human interleukin-11 receptor, cDNA sequences, recombinant production, and receptor inhibitors
INVENTOR(S): Tobin, James F.
PATENT ASSIGNEE(S): Genetics Institute, Inc., USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9619574	A1	19960627	WO 1995-US15400	19951127
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2208457	AA	19960627	CA 1995-2208457	19951127
AU 9644100	A1	19960710	AU 1996-44100	19951127
AU 717928	B2	20000406		
EP 797664	A1	19971001	EP 1995-942913	19951127
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 10511266	T2	19981104	JP 1995-519803	19951127
PRIORITY APPLN. INFO.:			US 1994-362304	19941222
			WO 1995-US15400	19951127

AB Polynucleotides encoding the human IL-11 receptor and fragments thereof are disclosed. Il-11 receptor proteins, methods for their prodn., inhibitors of binding of human IL-11 and its receptor and methods for their identification are also disclosed.
IT **168461-35-6P 179310-38-4P 179310-39-5P 179310-40-8P 179310-41-9P 179310-42-0P 179310-43-1P**
RL: BPN (Biosynthetic preparation); BPR (Biological process); PRP (Properties); BIOL (Biological study); PREP (Preparation); PROC (Process)
(amino acid sequence; human interleukin-11 receptor, cDNA sequences, recombinant prodn., and receptor inhibitors)

L19 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:342229 HCAPLUS
DOCUMENT NUMBER: 125:8495
TITLE: Cloning of cDNA for novel hemopoietin receptors of mammals
INVENTOR(S): Hilton, Douglas James
PATENT ASSIGNEE(S): Amrad Operations Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9607737	A1	19960314	WO 1995-AU578	19950905
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9534652	A1	19960327	AU 1995-34652	19950905
AU 690743	B2	19980430		
EP 804576	A1	19971105	EP 1995-931079	19950905
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
JP 10505068	T2	19980519	JP 1995-509002	19950905
CA 2197873	AA	19960314	CA 1995-2197873	19950909
PRIORITY APPLN. INFO.:			AU 1994-7901	19940905
			AU 1994-7902	19940905
			WO 1995-AU578	19950905

AB The cDNA encoding .alpha.-chain of interleukin 11 are isolated from mouse and human and their amino acid sequences deduced. The novel receptors contain a 5-amino-acid motif, WSXWS. The receptor mols. or components or parts thereof and their genetic sequences of the present invention are useful in the development of a wide range of agonists, antagonists and therapeutics and diagnostic reagents based on ligand interaction with its receptor.

IT **159994-99-7**
RL: PRP (Properties)
(amino acid sequence; cloning of cDNA for novel hemopoietin receptors of mammals)

IT **174129-57-8**
RL: PRP (Properties)
(nucleotide sequence; cloning of cDNA for novel hemopoietin receptors of mammals)

L19 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:114524 HCAPLUS
DOCUMENT NUMBER: 124:199986
TITLE: The human IL-11 receptor requires gp130 for signaling: demonstration by molecular cloning of the receptor
AUTHOR(S): Nandurkar, Harshal H.; Hilton, Douglas J.; Nathan, Paula; Willson, Tracy; Nicola, Nicos; Begley, C. Glenn
CORPORATE SOURCE: The Royal Melbourne Hospital, Victoria, 3050, Australia
SOURCE: Oncogene (1996), 12(3), 585-93
CODEN: ONCNES; ISSN: 0950-9232
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors describe the mol. cloning of a cDNA for the .alpha. chain of the human IL-11 receptor (IL-11r.alpha.) and demonstrate the requirement of either the human or mouse gp130 mol. for signaling. The cDNA clones encoding IL-11R.alpha. were isolated from a bone marrow cDNA library using a fragment from the murine IL-11R.alpha. as a probe. The human receptor was predicted to consist of 422 amino acids and was found to share 84% identity with the murine protein. In the extracellular region it exhibited a single hemopoietin domain with conserved cysteine residues and

WSTWS motif. The transmembrane region was followed by a short cytoplasmic tail which did not contain a tyrosine kinase domain. Interaction of the human IL-11R.alpha. with murine gp130 was demonstrated: expression of the human IL-11R.alpha. in murine M1 cells which constitutively express murine gp130 (and murine LIF receptor), resulted in the generation of specific high-affinity binding sites for IL-11 (Kd = 250 pM). In addn., expression of the human IL-11R.alpha. in these cells permitted the induction of macrophage differentiation in response to IL-11. These results suggested that the human IL-11R.alpha. chain was able to form a functional receptor complex in assocn. with murine gp130. The requirement of gp130 for signaling was confirmed by expression of the human IL-11R.alpha. in Ba/F3 cells. Ba/F3 cells that expressed the human IL-11R.alpha. alone showed binding of radiolabeled IL-11 but no proliferative response. Introduction of human gp130 into these cells resulted in high-affinity IL-11 binding sites and IL-11 dependent cellular proliferation. Thus these results demonstrated the abs. requirement of gp130 for signaling.

IT **174129-57-8**
RL: PRP (Properties)
(amino acid sequence; sequence of human IL-11 receptor .alpha.-chain cDNA and requirement of gp130 for signaling in induction of macrophage differentiation and proliferation)

L19 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:78800 HCAPLUS
DOCUMENT NUMBER: 124:143248
TITLE: Molecular cloning and characterization of the human interleukin-11 receptor .alpha.-chain gene, IL11RA, located on chromosome 9p13
AUTHOR(S): Van Leuven, Fred; Stas, Lou; Hilliker, Carl; Miyake, Yoshimasa; Bilinski, Petra; Grossler, Achim
CORPORATE SOURCE: Department of Human Genetics, Katholieke Universiteit Leuven, Louvain, B-3000, Belg.
SOURCE: Genomics (1996), 31(1), 65-70
CODEN: GNMCEP; ISSN: 0888-7543
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The human gene coding for the interleukin-11 receptor (IL11RA) was cloned and its structure analyzed. The gene is composed of 13 exons comprising nearly 10 kb of DNA that was completely sequenced. The intron-exon boundaries were detd. based on the mouse Etl2 and interleukin-11 receptor cDNAs that were recently cloned. The protein sequence predicted by the human gene was over 83% identical with its murine counterpart, with very strict conservation of functionally important domains and signatures. Fluorescence in situ hybridization showed the gene to be located on human chromosome 9p13, syntenic with the mouse etl2 gene on chromosome 4. The coding exons of the interleukin-11 gene were sequenced in a patient with the cartilage-hair hypoplasia syndrome, which has been linked to a gene on chromosome 9, but no functional mutations were detected.

IT **168461-35-6**
RL: PRP (Properties)
(amino acid sequence; sequence of human interleukin-11 receptor .alpha.-chain gene, IL11RA, located on chromosome 9p13 and lack of mutation in patient with cartilage-hair hypoplasia syndrome)

L19 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:827296 HCAPLUS

DOCUMENT NUMBER: 123:337025
TITLE: Molecular cloning of two isoforms of a receptor for the human hematopoietic cytokine interleukin-11
AUTHOR(S): Cherel, Michel; Sorel, Michel; Lebeau, Benoit; Dubois, Sigrid; Moreau, Jean-Francois; Bataille, Regis; Minvielle, Stephane; Jacques, Yannick
CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Centre Hospitalier Universitaire, Fr.
SOURCE: Blood (1995), 86(7), 2534-40
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Interleukin-11 (IL-11) is a stromal cell-derived cytokine with multiple biol. activities on lymphohematopoietic cells. It belongs to a family of pleiotropic and redundant cytokines that use the gp130 transducing subunit in their high affinity receptors. By amplifying human cDNA libraries with oligonucleotide primers corresponding to the conserved WSXWS motif found in the hematopoietic cytokine receptor family, a novel cytokine receptor cDNA was identified that, based on high (82%) sequence homol. with the recently cloned murine IL-11 receptor, appears to encode the human IL-11 receptor. This receptor is a 422-amino acid protein contg. a signal peptide followed by extracellular, transmembrane, and cytoplasmic domains. The extracellular region has a two-domain structure homologous to those of the IL-6 and ciliary neurotrophic factor (CNTF) receptors: an Ig-like domain and a cytokine receptor-like domain. In addn., an isoform of the human IL-11 receptor that lacks the cytoplasmic domain was also identified. In agreement with the pleiotropic effects of IL-11 on different hematopoietic lineages and bone cells, IL-11 receptor transcripts were expressed by the myelogenous leukemia cell line K5662, the megakaryocytic leukemia cell line Mo7E, the erythroleukemia cell line TF1, and the osteosarcoma cell lines MG-63 and Saos-2.

IT **168461-35-6 168461-36-7**
RL: PRP (Properties)
(amino acid sequence; mol. cloning of two isoforms of receptor for human hematopoietic cytokine interleukin-11)

L19 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:301764 HCAPLUS
DOCUMENT NUMBER: 122:211783
TITLE: Etl2, a novel putative type-I cytokine receptor expressed during mouse embryogenesis at high levels in skin and cells with skeletogenic potential
AUTHOR(S): Neuhaus, Herbert; Bettenhausen, Berthold; Bilinski, Petra; Simon-Chazottes, Dominique; Guenet, Jean-Louis; Gossler, Achim
CORPORATE SOURCE: Max-Delbrueck-Laboratorium in der MPG, Koln, 50829, Germany
SOURCE: Dev. Biol. (1994), 166(2), 531-42
CODEN: DEBIAO; ISSN: 0012-1606
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The regulatory effects of signaling proteins like hormones, growth factors, and cytokines are mediated by specific cell surface receptors which are grouped into distinct families on the basis of structural criteria. This report describes the isolation and embryonic expression of a novel mouse gene, Etl2 (enhancer trap locus 2) which, based on its

deduced amino acid sequence, constitutes a new member of the cytokine type-I receptor family. Among type-I receptors Etl2 is most similar to the .alpha. subunits of the human ciliary neurotrophic factor (CNTF) receptor and the mouse interleukin-6 (IL6) receptor with 32 and 30% identical amino acids, resp. From Day 9 p.c. (postcoitum) onward low levels of Etl2 mRNA were detected in mesenchymal cells throughout the embryo and in parts of the nervous system, in particular in the ependymal linings of the spinal cord and the developing brain vesicles and in the neuronal layer of the retina. Highest levels of Etl2 expression were found on Day 12.5 p.c. in the craniofacial mesenchyme and during subsequent development in mesenchymal cells around all developing cartilages. At later stages, Etl2 transcripts were abundant in the dental papilla, the dermis, and hair follicles, as well as in the perichondrium and periost, i.e., in regions contg. chondro and osteo progenitor cells. Etl2 mRNA was not detected, however, in mature odontoblasts, chondroblasts, osteoblasts, chondrocytes, or osteocytes. The results suggest that Etl2 is a new orphan receptor belonging to the type-I cytokine receptor family and that Etl2 might have regulatory functions, particularly in the control of proliferation and/or differentiation of skeletogenic progenitor and other mesenchymal cells.

IT **161631-14-7**
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(amino acid sequence; Etl2, a novel putative type-I cytokine receptor expressed during mouse embryogenesis at high levels in skin and cells with skeletogenic potential)

L19 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:199187 HCAPLUS
DOCUMENT NUMBER: 122:48118
TITLE: Cloning of a murine IL-11 receptor .alpha.-chain; requirement for gp130 for high affinity binding and signal transduction
AUTHOR(S): Hilton, Douglas J.; Hilton, Adrienne A.; Raicevic, Anna; Rakar, Steven; Harrison-Smith, Maria; Gough, Nicholas M.; Begley, C. Glenn; Metcalf, Donald; Nicola, Nicos; Willson, Tracy A.
CORPORATE SOURCE: Cooperative Res. Cent. Cell. Growth Factors, Walter Eliza Hall Inst. Med. Res., Parkville, Australia
SOURCE: EMBO J. (1994), 13(20), 4765-75
CODEN: EMJODG; ISSN: 0261-4189
DOCUMENT TYPE: Journal
LANGUAGE: English

AB An adult mouse liver cDNA library was screened with oligonucleotides corresponding to the conserved WSXWS motif of the haemopoietin receptor family. Using this method, cDNA clones encoding a novel receptor were isolated. The new receptor, named NR1, was most similar in sequence and predicted structure to the .alpha.-chain of the IL-6 receptor and mRNA was expressed in the 3T3-L1 pre-adipocytic cell line and in a range of primary tissues. Expression of NR1 in the factor-dependent haemopoietic cell line Ba/F3 resulted in the generation of low-affinity receptors for IL-11 (Kd .apprxeq. 10 nM). The capacity to bind IL-11 with high affinity (Kd = 300-800 pM) appeared to require coexpression of both NR1 and gp130, the common subunit of the IL-6, leukemia inhibitory factor (LIF), oncostatin M (OSM) and ciliary neurotrophic factor (CNTF) receptors. The expression of both NR1 and gp130 was also necessary for Ba/F3 cells to proliferate and

M1 cells to undergo macrophage differentiation in response to IL-11.
IT **159994-99-7**
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(cloning and sequence of murine IL-11 receptor .alpha.-chain and requirement for gp130 for high affinity binding and signal transduction)

=> fil reg

FILE 'REGISTRY' ENTERED AT 16:51:47 ON 23 FEB 2001
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=> d l18 rn cn lc nte sql kwic can tot

L18 ANSWER 1 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 251306-41-9 REGISTRY
CN 6: PN: WO9959608 SEQID: 3 unclaimed protein (9CI) (CA INDEX NAME)
LC STN Files: CA, CAPLUS
SQL 379

SEQ 201 LGASTCLLDV RLQSILRPDP PQGLRVESVP SYPRRLHASW TYPASWRRQP
======= ==========
HITS AT: 214-230

REFERENCE 1: 132:2795

L18 ANSWER 2 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 251306-40-8 REGISTRY
CN 5: PN: WO9959608 SEQID: 9 unclaimed protein (9CI) (CA INDEX NAME)
LC STN Files: CA, CAPLUS
NTE

type	------ location ------		description
uncommon	Aaa-18	-	-

SQL 20

SEQ 1 SILRPDPPQG LRVESVPXYP
========== =======

HITS AT: 1-17

REFERENCE 1: 132:2795

L18 ANSWER 3 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 251306-39-5 REGISTRY
CN 4: PN: WO9959608 SEQID: 7 unclaimed protein (9CI) (CA INDEX NAME)
LC STN Files: CA, CAPLUS
NTE

type	------ location ------		description
uncommon	Aaa-4	-	-

SQL 7

SEQ 1 RRLXASW
=======
HITS AT: 1-7

REFERENCE 1: 132:2795

L18 ANSWER 4 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 250688-39-2 REGISTRY
CN L-Proline, L-seryl-L-isoleucyl-L-leucyl-L-arginyl-L-prolyl-L-.alpha.-aspartyl-L-prolyl-L-prolyl-L-glutaminylglycyl-L-leucyl-L-arginyl-L-valyl-L-.alpha.-glutamyl-L-seryl-L-valyl-L-prolyl-L-seryl-L-tyrosyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 4: PN: WO9959608 SEQID: 8 claimed sequence
LC STN Files: CA, CAPLUS
SQL 20

SEQ 1 SILRPDPPQG LRVESVPSYP
========== =======
HITS AT: 1-17

REFERENCE 1: 132:2795

L18 ANSWER 5 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 250688-37-0 REGISTRY
CN L-Proline, L-seryl-L-isoleucyl-L-leucyl-L-arginyl-L-prolyl-L-.alpha.-aspartyl-L-prolyl-L-prolyl-L-glutaminylglycyl-L-leucyl-L-arginyl-L-valyl-L-.alpha.-glutamyl-L-seryl-L-valyl-L-prolylglycyl-L-tyrosyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3: PN: WO9959608 SEQID: 6 claimed sequence
LC STN Files: CA, CAPLUS
SQL 20

SEQ 1 SILRPDPPQG LRVESVPGYP
========== =======
HITS AT: 1-17

REFERENCE 1: 132:2795

L18 ANSWER 6 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 186004-58-0 REGISTRY
CN Interleukin 11 receptor (mouse gene IL11R.beta.) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 10: PN: WO0073451 SEQID: 10 unclaimed protein
CN GenBank U69491-derived protein GI 1916004
CN GenBank X98519-derived protein GI 1654014
CN Interleukin 11 receptor (mouse strain CD-1 gene IL11Ra2 .alpha.-chain precursor reduced)
LC STN Files: CA, CAPLUS, TOXLIT
SQL 432

SEQ 201 LGASTCLLDV RLQSILRPDP PQGLRVESVP GYPRRLHASW TYPASWRRQP
=======
HITS AT: 214-230

REFERENCE 1: 134:28451

REFERENCE 2: 126:289609

REFERENCE 3: 126:127547

L18 ANSWER 7 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 179310-43-1 REGISTRY
CN 112-365-Receptor, interleukin 11 (human clone phIL11R14-2 precursor) (9CI) (CA INDEX NAME)
LC STN Files: CA, CAPLUS
SQL 254

SEQ 101 LQSILRPDPP QGLRVESVPG YPRRLRASWT YPASWPCQPH FLLKFRLQYR
========
HITS AT: 103-119

REFERENCE 1: 125:140563

L18 ANSWER 8 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 179310-42-0 REGISTRY
CN 112-422-Receptor, interleukin 11 (human clone phIL11R14-2 precursor) (9CI) (CA INDEX NAME)
LC STN Files: CA, CAPLUS
SQL 311

SEQ 101 LQSILRPDPP QGLRVESVPG YPRRLRASWT YPASWPCQPH FLLKFRLQYR
========
HITS AT: 103-119

REFERENCE 1: 125:140563

L18 ANSWER 9 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 179310-41-9 REGISTRY
CN 102-365-Receptor, interleukin 11 (human clone phIL11R14-2 precursor) (9CI) (CA INDEX NAME)
LC STN Files: CA, CAPLUS
SQL 264

SEQ 101 GASTRLLDVS LQSILRPDPP QGLRVESVPG YPRRLRASWT YPASWPCQPH

```
                        ======== =========
HITS AT:    113-129

REFERENCE   1:  125:140563

L18  ANSWER 10 OF 17  REGISTRY  COPYRIGHT 2001 ACS
RN   179310-40-8  REGISTRY
CN   102-422-Receptor, interleukin 11 (human clone phIL11R14-2 precursor) (9CI)
     (CA INDEX NAME)
LC   STN Files:   CA, CAPLUS
SQL  321

SEQ    101 GASTRLLDVS LQSILRPDPP QGLRVESVPG YPRRLRASWT YPASWPCQPH
                      ======== =========
HITS AT:    113-129

REFERENCE   1:  125:140563

L18  ANSWER 11 OF 17  REGISTRY  COPYRIGHT 2001 ACS
RN   179310-39-5  REGISTRY
CN   24-365-Receptor, interleukin 11 (human clone phIL11R14-2 precursor) (9CI)
     (CA INDEX NAME)
LC   STN Files:   CA, CAPLUS
SQL  342

SEQ    151 PLGAARCVVH GAEFWSQYRI NVTEVNPLGA STRLLDVSLQ SILRPDPPQG
                                                      ==========
       201 LRVESVPGYP RRLRASWTYP ASWPCQPHFL LKFRLQYRPA QHPAWSTVEP
           =======
HITS AT:    191-207

REFERENCE   1:  125:140563

L18  ANSWER 12 OF 17  REGISTRY  COPYRIGHT 2001 ACS
RN   179310-38-4  REGISTRY
CN   24-422-Receptor, interleukin 11 (human clone phIL11R14-2 precursor) (9CI)
     (CA INDEX NAME)
LC   STN Files:   CA, CAPLUS
SQL  399

SEQ    151 PLGAARCVVH GAEFWSQYRI NVTEVNPLGA STRLLDVSLQ SILRPDPPQG
                                                      ==========
       201 LRVESVPGYP RRLRASWTYP ASWPCQPHFL LKFRLQYRPA QHPAWSTVEP
           =======
HITS AT:    191-207

REFERENCE   1:  125:140563

L18  ANSWER 13 OF 17  REGISTRY  COPYRIGHT 2001 ACS
RN   174129-57-8  REGISTRY
CN   Receptor, interleukin 11 (human clone 17.1 gene IL11RA .alpha.-chain
     precursor) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Interleukin-11-receptor-(human-clone-17.1-gene-IL11RA-.alpha.-chain
     precursor)
LC   STN Files:   CA, CAPLUS
```

SQL 422

SEQ 201 LGASTRLLDV SLQSILRPDP PQGLRVESVP GYPRRLRASW TYPASWPCQP
=======
HITS AT: 214-230

REFERENCE 1: 125:8495

REFERENCE 2: 124:199986

L18 ANSWER 14 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 168461-36-7 REGISTRY
CN Receptor, interleukin 11 (human clone HCR2 isoform precursor C-terminal fragment) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Interleukin 11 receptor (human clone HCR2 isoform precursor C-terminal fragment)
LC STN Files: CA, CAPLUS
SQL 388

SEQ 201 ASTRLLDVSL QSILRPDPPQ GLRVESVPGY PRRLRASWTY PASWPCQPHF
=========
HITS AT: 212-228

REFERENCE 1: 123:337025

L18 ANSWER 15 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 168461-35-6 REGISTRY
CN Receptor, interleukin 11 (human clone HCR1 precursor) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 11: PN: WO0073451 SEQID: 11 unclaimed protein
CN Interleukin 11 receptor (human clone HCR1 precursor)
CN Interleukin 11 receptor (human gene IL11RA .alpha.-chain precursor)
CN Receptor, interleukin 11 (human clone phIL11R14-2 precursor)
CN Receptor, interleukin 11 (human gene IL11RA .alpha.-chain precursor)
LC STN Files: CA, CAPLUS
SQL 422

SEQ 201 LGASTRLLDV SLQSILRPDP PQGLRVESVP GYPRRLRASW TYPASWPCQP
=======
HITS AT: 214-230

REFERENCE 1: 134:28451

REFERENCE 2: 125:140563

REFERENCE 3: 124:143248

REFERENCE 4: 123:337025

L18 ANSWER 16 OF 17 REGISTRY COPYRIGHT 2001 ACS
RN 161631-14-7 REGISTRY
CN Receptor, cytokine (Mus musculus clone .lambda.Et12g1 gene Et12) (9CI) (CA INDEX NAME)
LC STN Files: CA, CAPLUS

```
SQL  432

SEQ    201 LGASTCLLDV RLQSILRPDP PQGLRVESVP GYPRRLHASW TYPASWRRQP
                       ======= ==========
HITS AT:   214-230

REFERENCE   1:  122:211783

L18  ANSWER 17 OF 17  REGISTRY  COPYRIGHT 2001 ACS
RN   159994-99-7  REGISTRY
CN   Receptor, interleukin 11 (mouse clone NR1-AZ36 .alpha.-chain precursor)
     (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Interleukin 11 receptor (mouse gene IL11R.alpha.)
CN   Receptor NR1 (mouse liver clone NR1-AZ36 interleukin 11 .alpha.-chain
     precursor)
LC   STN Files:   CA, CAPLUS, TOXLIT
SQL  432

SEQ    201 LGASTCLLDV RLQSILRPDP PQGLRVESVP GYPRRLHASW TYPASWRRQP
                       ======= ==========
HITS AT:   214-230

REFERENCE   1:  126:127547

REFERENCE   2:  125:8495

REFERENCE   3:  122:48118


=> d stat que

L1            1 SEA FILE=REGISTRY "IL 11"/CN
L2           15 SEA FILE=REGISTRY INTERLEUKIN 11?/CN
L3            5 SEA FILE=REGISTRY ("INTERLEUKIN 11 RECEPTOR (HUMAN CLONE 17.1
                  GENE IL11RA .ALPHA.-CHAIN PRECURSOR)"/CN OR "INTERLEUKIN 11
                  RECEPTOR (HUMAN CLONE HCR1 PRECURSOR)"/CN OR "INTERLEUKIN 11
                  RECEPTOR (HUMAN CLONE HCR2 ISOFORM PRECURSOR C-TERMINAL
                  FRAGMENT)"/CN OR "INTERLEUKIN 11 RECEPTOR (HUMAN GENE IL11RA
                  .ALPHA.-CHAIN PRECURSOR)"/CN OR "INTERLEUKIN 11 RECEPTOR
                  (MOUSE GENE IL11R.ALPHA.)"/CN OR "INTERLEUKIN 11 RECEPTOR
                  (MOUSE GENE IL11R.BETA.)"/CN OR "INTERLEUKIN 11 RECEPTOR
                  (MOUSE STRAIN CD-1 GENE IL11RA2 .ALPHA.-CHAIN PRECURSOR
                  REDUCED)"/CN)
L4           10 SEA FILE=REGISTRY L2 NOT L3
L5            2 SEA FILE=REGISTRY ("GP130 (CHICKEN)"/CN OR "GP130 (HUMAN)"/CN)

L6            1 SEA FILE=REGISTRY "GP 130"/CN
L7            1 SEA FILE=REGISTRY "GLYCOPROTEIN 130 (HUMAN HEPG2 CELL)"/CN
L8         1014 SEA FILE=HCAPLUS L1 OR L4 OR (IL OR INTERLEUKIN)(W)11
L10         100 SEA FILE=HCAPLUS L3 OR (IL OR INTERLEUKIN)(W)(11R OR 11(W)(R
                  OR RECEPTOR?))
L11        1167 SEA FILE=HCAPLUS L5 OR L6 OR L7 OR GP130 OR GP(W)130
L12          42 SEA FILE=HCAPLUS L8 AND L10 AND L11
L14          12 SEA FILE=HCAPLUS L12 AND (?OSTEO? OR ?OSTEOPOROS? OR BONE? OR
                  BONY)
```

L15 4 SEA FILE=HCAPLUS (L12 AND (MUTAT? OR ALTER? OR CHANG?)) NOT L14
L18 17 SEA FILE=REGISTRY SILRPDPPQGLRVESVP|RRLXASW/SQSP
L19 11 SEA FILE=HCAPLUS L18
L21 58 SEA FILE=HCAPLUS (L8 OR L10)(L)((ANTIBOD? OR AB# OR MAB# OR PAB#)(5A)ANTI)
L22 56 SEA FILE=HCAPLUS L21 NOT (L15 OR L19 OR L14)
L23 9 SEA FILE=HCAPLUS L22 AND (?OSTEO? OR BONE? OR MENOPAUS? OR MENSTR? OR TERTIARY)

=> d ibib abs hitrn l23 1-9

L23 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:598279 HCAPLUS
TITLE: Interleukin-4 inhibits interleukin-11 production by rheumatoid synovial cells
AUTHOR(S): Taki, H.; Sugiyama, E.; Kuroda, A.; Mino, T.; Kobayashi, M.
CORPORATE SOURCE: First Department of Internal Medicine, Toyama Medical and Pharmaceutical University, Toyama, 930-0194, Japan
SOURCE: Rheumatology (Oxford) (2000), 39(7), 728-731
CODEN: RUMAFK; ISSN: 1462-0324
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective. To examine the effect of interleukin-4 (IL-4) on **IL-11** prodn. by rheumatoid synovial cells. Methods. Freshly isolated rheumatoid synovial cells (FRS) were obtained by collagenase digestion of rheumatoid arthritis (RA) synovial tissue specimens taken at the time of operation. Rheumatoid synovial cells at four to eight passages were used as cultured rheumatoid synovial fibroblasts (RSF). **IL-11** concn. was measured by ELISA. Results. IL-4 inhibited the prodn. of **IL-11** by FRS in a dose-dependent manner. This inhibition was obsd. in FRS obtained from six patients, and the mean inhibition was 46.5%. The inhibitory effect of IL-4 on **IL-11** prodn. was cancelled by the addn. of **anti**-IL-4 **antibody**. IL-4 also inhibited **IL-11** prodn. by IL-1.alpha.-stimulated cultured RSF. Conclusion. IL-4 inhibited **IL-11** prodn. by rheumatoid synovial cells. IL-4 has a protective effect on **bone** resorption. On the contrary, **IL-11** participates in **bone** resorption via **osteoclastogenesis**. Therefore, IL-4 may exert its protective effect on **bone** resorption, at least in part, via inhibition of **IL-11** prodn. in rheumatoid joints.
REFERENCE COUNT: 35
REFERENCE(S): (1) Allen, J; J Immunol 1993, V151, P4344 HCAPLUS
(3) Baumann, H; J Biol Chem 1991, V266, P20424 HCAPLUS
(5) Chomarat, P; J Immunol 1995, V154, P1432 HCAPLUS
(6) Colotta, F; Science 1993, V261, P472 HCAPLUS
(7) Elias, J; J Biol Chem 1994, V269, P22261 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:47203 HCAPLUS

DOCUMENT NUMBER: 133:16125
TITLE: Fluid shear stress increases interleukin-11 expression in human **osteoblast**-like cells: its role in **osteoclast** induction
AUTHOR(S): Sakai, Kenji; Mohtai, Masaaki; Shida, Jun-Ichi; Harimaya, Katsumi; Benvenuti, Susanna; Brandi, Maria L.; Kukita, Toshio; Iwamoto, Yukihide
CORPORATE SOURCE: Department of Orthopaedic Surgery, Faculty of Medicine, Kyushu University, Fukuoka, Japan
SOURCE: J. Bone Miner. Res. (1999), 14(12), 2089-2098
CODEN: JBMREJ; ISSN: 0884-0431
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It is unclear how mech. stress influences **bone** cells. Mech. stress causes fluid shear stress (FSS) in the **bone**. **Osteoblast** lineage cells are thought to sense FSS and regulate **bone** remodeling. We therefore investigated the effects of FSS on human **osteoblast**-like **osteosarcoma** cells: SaOS-2 cells in vitro. The conditioned medium of the SaOS-2 cells after 24 h of FSS (24 h-FSS CM) showed such **osteoclastic** phenotype inductions as significantly increasing the no. of tartrate-resistant acid phosphatase (TRAP) pos. multinuclear cells in rat **bone** marrow cells and TRAP-pos. cells in human **preosteoclastic** cells: FLG 29.1 cells. An ELISA showed **interleukin-11** (**IL-11**) protein to increase 7-fold in the 24 h-FSS CM. A Northern anal. showed that **IL-11** mRNA increased 4-fold in the SaOS-2 cells after 6 h-FSS; however, no IL-6 mRNA expression was detected. Furthermore, the **anti**-human **IL-11** **antibody** significantly neutralized the **osteoclastic** phenotype induction of the 24 h-FSS CM. The **IL-11** mRNA up-regulation in SaOS-2 cells by the 6 h-FSS was not inhibited by the anti-human transforming growth factor-.beta.1 antibody, but it was significantly inhibited by indomethacin. An enzymeimmunoassay showed prostaglandin E2 to increase 7-fold in the 1 h-FSS CM. These findings thus suggest that FSS induces **osteoblasts** to produce **IL-11** (mediated by prostaglandins) and thus stimulates **bone** remodeling.

REFERENCE COUNT: 36
REFERENCE(S):
(1) Ajubi, N; Biochem Biophys Res Commun 1996, V225, P62 HCAPLUS
(3) Bellido, T; Endocrinology 1997, V138, P3666 HCAPLUS
(4) Bellido, T; J Biol Chem 1998, V273, P21137 HCAPLUS
(5) Benvenuti, S; Biochem Biophys Res Commun 1994, V201, P1084 HCAPLUS
(6) Bonucci, E; Bone Miner 1992, V19, PS15 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:593091 HCAPLUS
DOCUMENT NUMBER: 129:301528
TITLE: Mode of action of interleukin-6 on mature **osteoclasts**. Novel interactions with extracellular Ca2+ sensing in the regulation of **osteoclastic bone** resorption

AUTHOR(S): Adebanjo, Olugbenga A.; Moonga, Baljit S.; Yamate, Tomoo; Sun, Li; Minkin, Cedric; Abe, Etsuko; Zaidi, Mone
CORPORATE SOURCE: Center for Osteoporosis and Skeletal Aging, Veterans Affairs Medical Center, Medical College of Pennsylvania-Hahnemann School of Medicine, Philadelphia, PA, 19104, USA
SOURCE: J. Cell Biol. (1998), 142(5), 1347-1356
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We describe a physiol. significant mechanism through which interleukin-6 (IL-6) and a rising ambient Ca2+ interact to regulate **osteoclastic bone** resorption. VOXEL-based confocal microscopy of nonpermeabilized **osteoclasts** incubated with **anti**-IL-6 receptor **antibodies** revealed intense, strictly peripheral plasma membrane fluorescence. IL-6 receptor expression in single **osteoclasts** was confirmed by in situ reverse transcriptase PCR histochem. IL-6 (5 ng/l to 10 .mu.g/l), but not **IL-11** (10 and 100 .mu.g/l), reversed the inhibition of **osteoclastic bone** resorption induced by high extracellular Ca2+ (15 mM). The IL-6 effect was abrogated by excess sol. IL-6 receptor (500 .mu.g/l). Addnl., IL-6 (5 pg/l to 10 .mu.g/l) inhibited cytosolic Ca2+ signals triggered by high Ca2+ or Ni2+. In sep. expts., **osteoclasts** incubated in 10 mM Ca2+ or on **bone** released more IL-6 than those in 1.25 mM Ca2+. Furthermore, IL-6 mRNA histostaining was more intense in **osteoclasts** in 10 or 20 mM Ca2+ than cells in 1.25 mM Ca2+. Similarly, IL-6 receptor mRNA histostaining was increased in **osteoclasts** incubated in 5 or 10 mM Ca2+. Thus, while high Ca2+ enhances IL-6 secretion, the released IL-6 attenuates Ca2+ sensing and reverses inhibition of resorption by Ca2+. Such an autocrine-paracrine loop may sustain **osteoclastic** activity in the face of an inhibitory Ca2+ level generated locally during resorption.

L23 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:333907 HCAPLUS
DOCUMENT NUMBER: 127:32186
TITLE: Stimulation of interleukin-11 production from **osteoblast**-like cells by transforming growth factor-.beta. and tumor cell factors
AUTHOR(S): Morinaga, Yoshihiro; Fujita, Naoya; Ohishi, Kazuo; Tsuruo, Takashi
CORPORATE SOURCE: Institute of Molecular and Cellular Biosciences, University of Tokyo, Tokyo, 113, Japan
SOURCE: Int. J. Cancer (1997), 71(3), 422-428
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Bone** is one of the most common sites of metastasis in melanoma and breast cancer cells. Human melanoma (A375M) and human breast cancer (MDA-MB-231) cells form **osteolytic bone** metastasis in vivo when these tumor cells are injected into the left ventricles of BALB/c nude mice. These tumor cells promote **bone** resorption in the in vitro neonatal murine calvaria organ culture system by indirectly

stimulating the prodn. of a **bone** resorption-inducing factor (or factors) from human **osteoblast**-like cells. This secreted factor was identified as **interleukin-11** (**IL-11**). Although many cytokines and hormones were assocd. with **IL-11** prodn. from **osteoblasts**, transforming growth factor-.beta. (TGF-.beta.) was found to be involved in the promotion of **IL-11** prodn. from **osteoblasts**, because the addn. of a neutralizing **anti**-TGF-.beta. **antibody** decreased the prodn. of **IL-11**. However, these tumor cells did not produce TGF-.beta. by themselves. We found that they enhanced **IL-11** prodn. by activating latent TGF-.beta. produced from **osteoblast**-like cells. Our results indicate that metastatic tumor cells induce **osteolysis** by activating TGF-.beta., which leads **IL-11** prodn. from **osteoblasts** to promote **bone** resorption.

L23 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:355134 HCAPLUS
DOCUMENT NUMBER: 125:26907
TITLE: Ability of flt3 ligand to stimulate the in vitro growth of primitive murine hematopoietic progenitors is potently and directly inhibited by transforming growth factor-.beta. and tumor necrosis factor-.alpha.
AUTHOR(S): Jacobsen, Sten E. W.; Veiby, Ole Petter; Myklebust, June; Okkenhaug, Cecilie; Lyman, Stewart D.
CORPORATE SOURCE: Blood Cell Growth Factors, Hipple Cancer Research Center, Dayton, OH, 45439-2092, USA
SOURCE: Blood (1996), 87(12), 5016-5026
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The recently cloned flt3 ligand (FL) stimulates the growth of primitive hematopoietic progenitor cells through synergistic interactions with multiple other cytokines. The present study is the first demonstrating cytokines capable of inhibiting Fl-stimulating hematopoietic cell growth. Tumor necrosis factor-.alpha. (TNF-.alpha.) and transforming growth factor-.beta.1 (TGF-.beta.1) potently inhibited the clonal growth of murine Lin- Sca-1+ **bone** marrow progenitors stimulated FL alone or in combination with granulocyte colony-stimulating factor (G-CSF), stem cell factor (SCF), interleukin (IL)-3, IL-6, **IL-11**, or IL-12. TGF-.beta.1 inhibited >96% of the myeloid colony formation in response to these cytokine combinations, whereas TNF-.alpha. reduced the no. of colonies by 58-96% depending on the cytokine by which FL was combined. In addn., both TNF-.alpha. and TGF-.beta.1 inhibited >90% of B220+ cell prodn. from B220- **bone** marrow cells stimulated by FL + IL-7. The effects of TNF-.alpha. and TGF-.beta.1 appeared to be due to a direct effect and on the early progenitors because the inhibition was obsd. at the single cell level, and because delayed addn. of the two inhibitors for only 48 h dramatically reduced their inhibitory effects. A neutralizing **anti**-TGF-.beta. **antibody** showed the presence of endogenous TGF-.beta. in the cultures and potently enhanced the ability of FL to stimulate progenitor cell growth in the absence of other cytokines. Agonistic antibodies specifically activating the p75 TNF receptors were more efficient than wild-type murine TNF-.alpha. in signaling growth inhibition of Lin-Sca-1+ progenitor cells, whereas the p55 agonist had less effect than murine TNF-.alpha.. Finally, TGF-.beta.

increased the no. of FL + **IL-11**-stimulated Lin- Sca-1+ cells in the G1 phase of the cell cycle with 76%, whereas TNF-.alpha. only had a marginal effect on cell cycle distribution. Thus, TGF-.beta., TNF-.alpha., and p75 TNF receptor agonists are potent direct inhibitors of FL-stimulated progenitor cell growth in vitro.

L23 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:790083 HCAPLUS
DOCUMENT NUMBER: 123:254138
TITLE: Direct synergistic effects of IL-4 and IL-11 on proliferation of primitive hematopoietic progenitor cells
AUTHOR(S): Jacobsen, Frede W.; Keller, Jonathan R.; Ruscetti, Francis W.; Veiby, Ole P.; Jacobsen, Sten E. W.
CORPORATE SOURCE: Institute for Cancer Research, Norwegian Radium Hospital, Oslo, 0310, Norway
SOURCE: Exp. Hematol. (Charlottesville, Va.) (1995), Volume Date 1995, 23(9), 990-5
CODEN: EXHMA6; ISSN: 0301-472X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present studies investigated, for the first time, the synergistic effects of interleukin-4 (IL-4) and **IL-11** on the growth of single murine **bone** marrow progenitor cells. The studies suggest that IL-4 and **IL-11** are synergistic hematopoietic growth factors, enhancing colony formation of **bone** marrow progenitors from normal mice in the presence of colony-stimulating factors or stem cell factor, whereas neither IL-4 nor **IL-11**, alone or in combination, resulted in colony formation. However, in the presence of a neutralizing **anti**-TGF-.beta. **antibody**, **IL-11** plus IL-4 induced clonal growth of primitive Lin-Sca-1+ progenitors. Furthermore, the authors report several observations extending the knowledge about IL-4 and **IL-11** as synergistic factors. In addn. to the established ability of **IL-11** to enhance IL-3- and GM-CSF-induced colony formation, **IL-11** also enhanced the no. of G-CSF- and CSF-1-stimulated colonies of mature (Lin-) and primitive (Lin-Sca-1+) hematopoietic progenitors cultured at the single-cell level. In contrast, IL-4 bifunctionally regulated the growth of Lin- progenitors, whereas the growth of single Lin-Sca-1+ progenitors was unaffected or enhanced in the presence of IL-4. Finally, IL-4 and **IL-11**, in combination, potently synergized to enhance the high proliferative-potential colony-forming cell colony formation of Lin-Sca-1+ progenitors in response to all 4 CSFs and to SCF.

L23 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:678940 HCAPLUS
DOCUMENT NUMBER: 123:75165
TITLE: Ovariectomy enhances and estrogen replacement inhibits the activity of **bone** marrow factors that stimulate prostaglandin production in cultured mouse calvariae
AUTHOR(S): Kawaguchi, Hiroshi; Pilbeam, Carol C.; Vargas, Socorro J.; Morse, Edward E.; Lorenzo, Joseph A.; Raisz, Lawrence G.
CORPORATE SOURCE: Division Endocrinology Metabolism, University

Connecticut Health Center, Farmington, CT, 06030, USA
SOURCE: J. Clin. Invest. (1995), 96(1), 539-48
CODEN: JCINAO; ISSN: 0021-9738
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To examine PG prodn. in estrogen deficiency, the authors studied effects on cultured neonatal mouse calvariae of **bone** marrow supernatants (MSup) from sham-operated (SHAM), ovariectomized (OVX), or 17.beta.-estradiol (OVX + E)-treated mice. MSups were obtained 3 wk after OVX when **bone** d. had decreased significantly. 10-60% MSup increased medium PGE2 and levels of mRNA for inducible and constitutive prostaglandin G/H synthase (PGHS-2 and PGHS-1) and cytosolic phospholipase A2 in calvarial cultures. OVX MSups had 2-fold greater effects on PGHS-2 and medium PGE2 than other MSups. IL-1 receptor antagonist and **anti**-IL-1.alpha. neutralizing **antibody** decreased MSup-stimulated PGHS-2 mRNA and PGE2 levels and diminished differences among OVX, sham-operated, and OVX + E groups. In contrast, antibodies to IL-1.beta., IL-6, **IL-11**, and TNF.alpha. had little effect. There were no significant differences in IL-1.alpha. concns. or IL-1.alpha. mRNA levels in MSups or marrow cells. PGHS-2 mRNA in freshly isolated tibiae from OVX mice was slightly greater than from sham-operated. The authors conclude that **bone** marrow factors can increase PG prodn. through stimulation of PGHS-2; that OVX increases and estrogen decreases activity of these factors; and that IL-1.alpha. activity, together with addnl. unknown factors, mediates the differential MSup effects.

L23 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:75172 HCAPLUS
DOCUMENT NUMBER: 120:75172
TITLE: Soluble interleukin-6 receptor triggers **osteoclast** formation by interleukin 6
AUTHOR(S): Tamura, Tatsuya; Udagawa, Nobuyuki; Takahashi, Naoyuki; Miyaura, Chisato; Tanaka, Sakae; Yamada, Yoshiki; Koishihara, Yasuo; Ohsugi, Yoshiyuki; Kumaki, Kenji; et al.
CORPORATE SOURCE: Sch. Dent., Showa Univ., Tokyo, 142, Japan
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(24), 11924-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It has been reported that sol. interleukin (IL)-6 receptor (sIL-6R) is detected in the serum of healthy individuals and its level is increased in patients with multiple myeloma and human immunodeficiency virus infection. Although several reports have suggested that sIL-6R potentiates IL-6 action, is physiol. role remains unclear. In this study, the authors examd. the role of sIL-6R on **osteoclast** formation by IL-6, using a coculture of mouse **osteoblasts** and **bone** marrow cells. Neither recombinant mouse IL-6 (mIL-6) nor mouse sIL-6R (smIL-6R) induced **osteoclast**-like multinucleated cell (MNC) formation when they were added sep. In contrast, simultaneous treatment with mIL-6 and smIL-6R strikingly induced MNC formation. These MNCs satisfied major criteria of authentic **osteoclasts**, such as tartrate-resistant acid phosphatase (TRAP) activity, calcitonin receptors, and pit formation on dentin slices. The MNC formation induced by mIL-6 and smIL-6R was

dose-dependently inhibited by adding monoclonal **anti**-mouse IL-6R **antibody** (MR16-1). It is likely that **osteoblasts** and **osteoclast** progenitors are capable of transducing a signal from a complex of IL-6 and sIL-6R through gp130, even though they may have no or a very small no. of IL-6Rs. Factors such as **IL-11**, oncostatin M, and leukemia inhibitory factor, which are known to exert their functions through gp130 (the signal-transducing chain of IL-6R), also induced MNC formation in the authors' coculture system. These results suggest that increased circulating or locally produced sIL-6R induces **osteoclast** formation in the presence of IL-6 mediated by a mechanism involving gp130. This may play an important physiol. or pathol. role in conditions assocd. with increased **osteoclastic bone** resorption.

L23 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:104117 HCAPLUS
DOCUMENT NUMBER: 116:104117
TITLE: Interleukin-11 enhances human megakaryocytopoiesis in vitro
AUTHOR(S): Teramura, Masanao; Kobayashi, Shoko; Hoshino, Shigeru; Oshimi, Kazuo; Mizoguchi, Hideaki
CORPORATE SOURCE: Dep. Med., Tokyo Women's Med. Coll., Tokyo, 162, Japan
SOURCE: Blood (1992), 79(2), 327-31
CODEN: BLOOAW; ISSN: 0006-4971
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect was investigated of recombinant human **interleukin-11** (rhIL-11) on human megakaryocytopoiesis. Nonadherent and T-cell-depleted human **bone** marrow (BM) mononuclear cells were cultured in a serum-free agar culture system. RhIL-11 alone did not stimulate the growth of human megakaryocyte colonies. However, when rhIL-11 was combined with optimal or suboptimal doses of rhIL-3, the no. and size of the megakaryocyte colonies increased. The same results were obtained when highly purified BM CD34-pos. cells were used as target cells. Next, the effect was investigated of rhIL-11 on the ploidy of megakaryocytes. The ploidy distribution of individual cells in megakaryocyte colonies obtained by rhIL-11 in combination with rhIL-3 was significantly shifted towards higher values. Furthermore, when highly purified CD41-pos. BM cells were cultured in the presence of rhIL-11, the ploidy distribution was shifted towards higher values. This effect was not suppressed by **anti**-IL-6 **antibody**. Thus, rhIL-11 acts directly as a megakaryocyte potentiator and may play a role in regulating human megakaryocytopoiesis.

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         (c) 2001 Inst for Sci Info
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             11(W)R OR RECEPTOR) OR (GP OR GLYCOPROTEIN?)(W)130
S2       2932   S1 AND (OSTEO? OR OSTEOPOROS? OR BONE? OR BONY)
S3         81   S2 AND (MENSTRUAL? OR POSTMENOPAUS? OR MENOPAUS?)
S4         46   RD (unique items)
S5          1   S4 AND TERTIARY
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?t s4/3 ab/1-46

 4/AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10394347   20253578
  Osteoprotegerin and its ligand: A new paradigm for regulation of
 osteoclastogenesis and bone resorption.
  Aubin JE; Bonnelye E
  Department of Anatomy and Cell Biology, University of Toronto, Ontario,
Canada.
  Medscape women's health (UNITED STATES) Mar 2000, 5 (2) p5, ISSN
1521-2076   Journal Code: C3A
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
  In just 3 years, striking new advances have been made in understanding
the molecular mechanisms that govern the crosstalk between osteoblasts
/stromal cells and hemopoietic osteoclast precursor cells that leads to
 osteoclastogenesis . Led first by the discovery of osteoprotegerin (OPG),
a naturally occurring protein with potent osteoclastogenesis inhibitory
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activity, rapid progress was made to the isolation of RANKL, a transmembrane ligand expressed on osteoblasts /stromal cells, that binds to RANK, a transmembrane receptor on hemopoietic osteoclast precursor cells. The interaction of RANK and RANKL initiates a signaling and gene expression cascade that results in differentiation and maturation of osteoclast precursor cells to active osteoclasts capable of resorbing bone . Osteoprotegerin acts as a decoy receptor; it binds to RANKL and blocks its interaction with RANK, thus inhibiting osteoclast development. Many of the calciotropic hormones and cytokines, including vitamin D3, parathyroid hormone, prostaglandin E2 and interleukin -11 , appear to stimulate osteoclastogenesis through the dual action of inhibiting production of OPG and stimulating production of RANKL. Estrogen, on the other hand, appears to inhibit production of RANKL and RANKL-stimulated osteoclastogenesis . Recently, the results of the first clinical trial with OPG supported its potential as a therapeutic agent for osteoporosis . The new understanding provided by the RANK/RANKL/OPG paradigm for both differentiation and activation of osteoclasts has had tremendous impact on the field of bone biology and has opened new avenues for development of possible treatments of diseases characterized by excessive bone resorption.

4/AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09534343 98289377

In vitro secretion of cytokines by human bone marrow: effects of age and estrogen status.

Cheleuitte D; Mizuno S; Glowacki J

Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.

Journal of clinical endocrinology and metabolism (UNITED STATES) Jun 1998, 83 (6) p2043-51, ISSN 0021-972X Journal Code: HRB

Contract/Grant No.: AG-12271, AG, NIA; AG-13519, AG, NIA

Languages: ENGLISH

Document type: JOURNAL ARTICLE

It has been proposed that cytokines mediate the acceleration of bone loss following menopause . Because of the intimate relationship between bone marrow stromal cells and bone tissue, it is possible that marrow cells and their products contribute to the bone microenvironment and influence the regulation of bone cell differentiation and activity. We examined the production of cytokines by bone marrow stromal cells from a total of 37 women and 15 men undergoing total hip replacement for noninflammatory joint disease. Low-density mononuclear cells were isolated from bone marrow and were cultured in phenol red-free alpha MEM medium supplemented with 10% FBS and antibiotics. Constitutive secretion of interleukin-6 (IL-6) was positively correlated with age in a series of 8 women and 5 men measured by bioassay ($r = 0.98$; $P < 0.01$) and in a series of 18 women and 10 men measured by immunoassay ($r = 0.56$; $P < 0.01$). The pattern of cytokine production by bone marrow stromal cells was examined in detail in 23 postmenopausal women, aged 49-88 yr. Basal secretion of immunoreactive IL-6 and IL - 11 , but not granulocyte-macrophage colony-stimulating factor, increased with time in culture. Exogenous IL-1 beta stimulated secretion of IL-6 and IL - 11 in a saturable, dose-dependent manner. Secretion of soluble IL-6 receptor was not correlated with secretion of IL-6, either constitutively or in the presence of IL-1 beta. In 4 of 14 samples, IL-1 beta also stimulated secretion of granulocyte-macrophage colony-stimulating factor. IL-1 beta was undetectable in 7 of 9 cultures during the 2-week culture period. IL-6 did not stimulate secretion of IL-1 beta in the 7 cultures tested. Cells were

dependent upon serum for viability and growth and were not sustained by a serum substitute (1% insulin-transferrin-selenium-BSA). Cells grown in medium with 10% FBS and supplemented with 1% insulin-transferrin-selenium-BSA secreted 10-fold more IL-6 than cells grown in serum alone. Marrow from 7 women receiving estrogen replacement therapy showed lower constitutive secretion of IL-6 (75%; P < 0.006) and IL - 11 (43%; P < 0.05) than marrow from age-matched controls and had blunted stimulation of IL-6 and IL -11 secretion by exogenous IL-1 beta. These data indicate distinct patterns of cytokine production by human marrow stromal cultures dependent upon age and estrogen status.

4/AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09406155 98124943
Immunologic aspects of osteoporosis.
Ershler WB; Harman SM; Keller ET
Gerontologic Research Center, National Institute on Aging, National Institutes of Health, Baltimore, Maryland 21224, USA.
Developmental and comparative immunology (UNITED STATES) Nov-Dec 1997, 21 (6) p487-99, ISSN 0145-305X Journal Code: E3M
Contract/Grant No.: AG11970, AG, NIA
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Osteoporosis is a major cause of morbidity in older people. There are a large number of risk factors for the development of osteoporosis . However, these risk factors eventually must mediate their effects through modulation of bone remodeling. A variety of compounds including hormones and nutrients modulate bone remodeling. In addition to these well-characterized substances, the immune system plays a role in bone remodeling through pro-inflammatory cytokines. Specifically, interleukin-1 (IL-1), IL - 11 , interferon-g are known to influence osteoclasts and osteoblasts . Recently, the cytokine IL-6 has joined ranks with these cytokines as a bone reactive agent. IL-6 has been shown to increase with age and menopause . Additionally, murine models suggest that IL-6 plays a central role in bone resorption. Finally, in vitro studies demonstrate that IL-6 induces osteoclast activity. In this review, we will discuss the pathogenesis of osteoporosis in the context of aging and IL-6.

4/AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09276027 97289981
Interleukin-6: structure-function relationships.
Simpson RJ; Hammacher A; Smith DK; Matthews JM; Ward LD
Joint Protein Structure Laboratory, Ludwig Institute for Cancer Research, (Melbourne Tumour Biology Branch), Parkville, Victoria, Australia. simpson@licre.ludwig.edu.au
Protein science (UNITED STATES) May 1997, 6 (5) p929-55, ISSN 0961-8368 Journal Code: BNW
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Interleukin-6 (IL-6) is a multifunctional cytokine that plays a central role in host defense due to its wide range of immune and hematopoietic activities and its potent ability to induce the acute phase response. Overexpression of IL-6 has been implicated in the pathology of a number of diseases including multiple myeloma, rheumatoid arthritis, Castleman's

disease, psoriasis, and post-menopausal osteoporosis . Hence, selective antagonists of IL-6 action may offer therapeutic benefits. IL-6 is a member of the family of cytokines that includes interleukin -11 , leukemia inhibitory factor, oncostatin M, cardiotrophin-1, and ciliary neurotrophic factor. Like the other members of this family, IL-6 induces growth or differentiation via a receptor-system that involves a specific receptor and the use of a shared signaling subunit, gp130. Identification of the regions of IL-6 that are involved in the interactions with the IL-6 receptor, and gp130 is an important first step in the rational manipulation of the effects of this cytokine for therapeutic benefit. In this review, we focus on the sites on IL-6 which interact with its low-affinity specific receptor, the IL-6 receptor, and the high-affinity converter gp130. A tentative model for the IL-6 hexameric receptor ligand complex is presented and discussed with respect to the mechanism of action of the other members of the IL-6 family of cytokines.

4/AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08664237 96219627
Human interleukin-6 receptor super-antagonists with high potency and wide spectrum on multiple myeloma cells.
Sporeno E; Savino R; Ciapponi L; Paonessa G; Cabibbo A; Lahm A; Pulkki K; Sun RX; Toniatti C; Klein B; et al
Istituto di Richerche di Biologia Molecolare (IRBM)- P. Angeletti, Pomezia, Rome, Italy.
Blood (UNITED STATES) Jun 1 1996, 87 (11) p4510-9, ISSN 0006-4971 Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Interleukin-6 (IL-6) is the major growth factor for myeloma cells and is believed to participate in the pathogenesis of chronic autoimmune diseases and postmenopausal osteoporosis . IL-6 has been recently shown to possess three topologically distinct receptor binding sites: site 1 for binding to the subunit specific chain IL-6R alpha and sites 2 and 3 for the interaction with two subunits of the signaling chain gp130. We have generated a set of IL-6 variants that behave as potent cytokine receptor super-antagonists carrying substitutions that abolish interaction with gp130 at either site 2 alone (site 2 antagonist) or at both sites 2 and 3 (site 2 + 3 antagonist). In addition, substitutions have been introduced in site 1 that lead to variable increases in binding for IL-6R alpha up to 70-fold. IL-6 super-antagonists inhibit wild-type cytokine activity with efficacy proportional to the increase in receptor binding on a variety of human call lines of different origin, and the most potent molecules display full antagonism at low molar excess to wild-type IL-6. When tested on a representative set of IL-6-dependent human myeloma cell lines, although site 2 super-antagonists were in general quite effective, only the site 2 + 3 antagonist Sant7 showed antagonism on the full spectrum of cells tested. In conclusion, IL-6 super-antagonists are a useful tool for the study of myeloma in vitro and might constitute, in particular Sant7, effective IL-6 blocking agents in vivo.

4/AB/6 (Item 6 from file: 155)
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08237240 95115719
Bone marrow, cytokines, and bone remodeling. Emerging insights into

the pathophysiology of osteoporosis.
Manolagas SC; Jilka RL
Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock 72205.
New England journal of medicine (UNITED STATES) Feb 2 1995, 332 (5) p305-11, ISSN 0028-4793 Journal Code: NOW
Contract/Grant No.: AR 41313, AR, NIAMS; AR 43003, AR, NIAMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Both osteoblasts and osteoclasts are derived from progenitors that reside in the bone marrow; osteoblasts belong to the mesenchymal lineage of the marrow stroma, and osteoclasts to the hematopoietic lineage. The development of osteoclasts from their progenitors is dependent on stromal- osteoblastic cells, which are a major source of cytokines that are critical in osteoclastogenesis , such as interleukin-6 and interleukin - 11 . The production of interleukin-6 by stromal osteoblastic cells, as well as the responsiveness of bone marrow cells to cytokines such as interleukin-6 and interleukin -11 , is regulated by sex steroids. When gonadal function is lost, the formation of osteoclasts as well as osteoblasts increases in the marrow, both changes apparently mediated by an increase in the production of interleukin-6 and perhaps by an increase in the responsiveness of bone marrow progenitor cells not only to interleukin-6 but also to other cytokines with osteoclastogenic and osteoblastogenic properties. The cellular activity of the bone marrow is also altered by the process of aging. Specifically, senescence may decrease the ability of the marrow to form osteoblast precursors. The association between the dysregulation of osteoclast or osteoblast development in the marrow and the disruption of the balance between bone resorption and bone formation, resulting in the loss of bone , leads to the following notion. Like homeostasis of other regenerating tissues, homeostasis of bone depends on the orderly replenishment of its cellular constituents. Excessive osteoclastogenesis and inadequate osteoblastogenesis are responsible for the mismatch between the formation and resorption of bone in postmenopausal and age-related osteopenia . The recognition that changes in the numbers of bone cells, rather than changes in the activity of individual cells, form the pathogenetic basis of osteoporosis is a major advance in understanding the mechanism of this disease.

4/AB/7 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11998124 BIOSIS NO.: 199900278643
Increased serum levels of osteoclast activating cytokines as a possible reason for osteoporosis in patients with common variable immunodeficiency (CVID).
AUTHOR: Junker U(a); Fichtler J; Nuske K; Vogelsang H
AUTHOR ADDRESS: (a)Institut fuer Klinische Immunologie, Klinikum der Friedrich-Schiller-Universitaet, Am Johannisfr**Germany
JOURNAL: Allergologie 22 (2):p108-112 Feb., 1999
ISSN: 0344-5062
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: German; Non-English
SUMMARY LANGUAGE: English; German

ABSTRACT: Increased serum levels of interleukin-6 (IL-6) have repeatedly been reported in patients suffering form CVID, and have been blamed to contribute to the osteoporotic process observed in these patients. In

fact, IL-6 is considered to be a major factor in osteoporosis in post-menopausal women and other conditions accompanied with loss of sex hormones. Recent investigations identified other cytokines using the gp130 signal transducer molecule, namely oncostatin M, leukemia inhibitory factor, ciliary neurotrophic factor, and most prominently interleukin -11 (IL -11) as major osteoclast -activating factors. Here we show that the extremly elevated levels of IL-6 reported in earlier works may be caused in part by IL -11 . Also, we report dramatically increased levels of IL -11 bioactivity and protein content in the sera of patients with CVID. We consider this to be additional proof that cytokines acting through gp130 play an essential role in osteoporosis in these patients and to warrant an investigation of other gp130-activating cytokines in CVID.

1999

4/AB/8 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11061828 BIOSIS NO.: 199799682973
The involvement of IL-6 receptor and gp130 in osteoclast differentiation and function in postmenopause.
AUTHOR: Gao Y(a); Morita I; Maruo N; Kubota T(a); Murota S; Aso T(a)
AUTHOR ADDRESS: (a)Dep. Obstetrics and Gynecol., Fac. Med., Tokyo Med. and Dent. Univ., Tokyo**Japan
JOURNAL: Maturitas 27 (SUPPL.):p143 1997
CONFERENCE/MEETING: 8th International Congress on the Menopause Sydney, Australia November 3-7, 1996
ISSN: 0378-5122
RECORD TYPE: Citation
LANGUAGE: English
1997

4/AB/9 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

08311004 Genuine Article#: 270DT Number of References: 48
Title: Suggestive linkage of the parathyroid receptor type 1 to osteoporosis (ABSTRACT AVAILABLE)
Author(s): Duncan EL; Brown MA (REPRINT) ; Sinsheimer J; Bell J; Carr AJ; Wordsworth BP; Wass JAH
Corporate Source: WELLCOME TRUST CTR HUMAN GENET,ROOSEVELT DR/HEADINGTON OX3 7BN//ENGLAND/ (REPRINT); WELLCOME TRUST CTR HUMAN GENET,/HEADINGTON OX3 7BN//ENGLAND/; ST VINCENTS HOSP,GARVAN INST MED RES, BONE & MINERAL RES PROGRAM/DARLINGHURST/NSW 2010/AUSTRALIA/; UNIV CALIF LOS ANGELES,DEPT BIOMATH/LOS ANGELES//CA/; UNIV CALIF LOS ANGELES,DEPT BIOSTAT/LOS ANGELES//CA/; JOHN RADCLIFFE HOSP,NUFFIELD DEPT CLIN MED/OXFORD OX3 9DU//ENGLAND/; NUFFIELD ORTHOPAED CTR,/HEADINGTON//ENGLAND/; RADCLIFFE INFIRM,DEPT ENDOCRINOL/OXFORD OX2 6HE//ENGLAND/
Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1999, V14, N12 (DEC), P 1993-1999
ISSN: 0884-0431 Publication date: 19991200
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148
Language: English Document Type: ARTICLE
Abstract: We have investigated the role of 23 candidate genes in the control of bone mineral density (BMD) by linkage studies in families

of probands with osteoporosis (lumbar spine [LS] or femoral neck [FN] BMD T score < -2.5) and low BMD relative to an age- and gender-matched cohort (Z score < -2.0). One hundred and fifteen probands (35 male, 80 female) and 499 of their first- or second-degree relatives (223 males and 276 females) were recruited for the study. BMD was measured at the LS and FN using dual-energy X-ray absorptiometry and expressed as age- and gender-matched Z scores corrected for body mass index. The candidate genes studied were the androgen receptor, type I collagen A1 (COLIA1), COLIA2, COLIIA1, vitamin D receptor (VDR), colony-stimulating factor 1, calcium-sensing receptor, epidermal growth factor (EGF), estrogen receptor 1 (ESR1), fibrillin type 1, insulin-like growth factor 1, interleukin-1 alpha (IL-1 alpha), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin -11 (IL -11), osteopontin , parathyroid hormone (PTH), PTH-related peptide, PTH receptor type 1 (PTHR1), transforming growth factor-beta 1, and tumor necrosis factors alpha and beta. Sixty-four microsatellites lying close to or within these genes were investigated for linkage with BMD. Using the program MapMaker/Sibs there was suggestive evidence of linkage between BMD and PTHR1 (maximum LOD score obtained [MLS] 2.7-3.5). Moderate evidence of linkage was also observed with EGF (MLS 1.8), COLIA1 (MLS 1.7), COLIIA1/VDR (MLS 1.7), ESR1 (MLS 1.4), IL-1 alpha (MLS 1.4), IL-4 (MLS 1.2), and IL-6 (MLS 1.2). Variance components analysis using the program ACT, correcting for proband-wise ascertainment, also showed evidence of linkage (p less than or equal to 0.05) at markers close to or within the candidate genes IL-1 alpha, PTHR1, IL-6, and COLIIA1/VDR. Further studies will be required to confirm these findings, to refine the location of gene responsible for the observed linkage, and to screen the candidate genes targeted at these loci for mutations.

4/AB/10 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06308234 Genuine Article#: YH190 Number of References: 53
Title: Interleukin-6 with its soluble receptor enhances the expression of insulin-like growth factor-I in osteoblasts (ABSTRACT AVAILABLE)
Author(s): Franchimont N; Gangji V; Durant D; Canalis E (REPRINT)
Corporate Source: ST FRANCIS HOSP & MED CTR,DEPT RES, 114 WOODLAND ST/HARTFORD//CT/06105 (REPRINT); ST FRANCIS HOSP & MED CTR,DEPT RES/HARTFORD//CT/06105; ST FRANCIS HOSP & MED CTR,DEPT MED/HARTFORD//CT/06105; UNIV CONNECTICUT,SCH MED/FARMINGTON//CT/06030
Journal: ENDOCRINOLOGY, 1997, V138, N12 (DEC), P5248-5255
ISSN: 0013-7227 Publication date: 19971200
Publisher: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110
Language: English Document Type: ARTICLE
Abstract: Interleukin (IL)-6, a cytokine produced by skeletal cells and known to increase bone resorption, has mitogenic effects for bone cells, pos sibly by regulating the synthesis of other local factors. We tested the effects of IL-6 and its soluble receptor (IL-6sR) on the expression of insulin-like growth factor (IGF)-I and IGF-II in cultured osteoblast -enriched cells from fetal rat calvariae (Ob cells). IL-6 did not modify IGF-I messenger RNA (mRNA) levels, but when tested in the presence of IL-6sR, IL-6 at 1 to 100 ng/ml increased IGF-I transcripts by up to 3.2-fold after 24 h. IL-6sR caused a small increase in IGF-I mRNA levels when tested alone. IL-6 and IL-6sR increased immunoreactive IGF-I levels by 2.4-fold after 24 h and 6.4-fold after 48 h. Cycloheximide prevented, and indomethacin markedly decreased, the effect of IL-6 and IL-6sR on IGF-I mRNA levels, but hydroxyurea did not. IL-6 and IL-6sR did not alter the decay of IGF-I

mRNA in transcriptionally arrested Ob cells, and the half-life of the predominant 6.5-kb IGF-I transcript was about 11 h in control and treated cells. In addition, IL-6 and IL-6sR increased the levels of IGF-I heterogeneous nuclear RNA. IL -11 also increased IGF-I mRNA levels, whereas oncostatin M and leukemia-inhibitory factor did not. In contrast to their effects on IGF-I, IL-6 and IL-6sR caused only a modest increase in IGF-II mRNA and polypeptide levels. In conclusion, IL-6, in the presence of IL-6sR, increases IGF-I synthesis in Ob cells; this effect may lead to a secondary increase in bone formation.

4/AB/11 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

06202738 Genuine Article#: YB479 Number of References: 22
Title: Osteoclasts are present in gp130-deficient mice (ABSTRACT AVAILABLE)
Author(s): Kawasaki K; Gao YH; Yokose S; Kaji Y; Nakamura T; Suda T; Yoshida K; Taga T; Kishimoto T; Kataoka H; Yuasa T; Norimatsu H; Yamaguchi A (REPRINT)
Corporate Source: SHOWA UNIV,SCH DENT, DEPT ORAL PATHOL, SHINAGAWA KU, 1-5-8 HATANODAI/TOKYO 142//JAPAN/ (REPRINT); SHOWA UNIV,SCH DENT, DEPT ORAL PATHOL, SHINAGAWA KU/TOKYO 142//JAPAN/; SHOWA UNIV,SCH DENT, DEPT BIOCHEM/TOKYO 142//JAPAN/; KAGAWA MED SCH,DEPT ORTHOPED SURG/KAGAWA 76107//JAPAN/; UNIV OCCUPAT & ENVIRONM HLTH,SCH MED, DEPT ORTHOPED SURG/FUKUOKA 807//JAPAN/; OSAKA UNIV,INST MOL & CELLULAR BIOL/OSAKA 565//JAPAN/; OSAKA UNIV,SCH MED, DEPT MED 3/OSAKA 565//JAPAN/; JUNTENDO UNIV,SCH MED, DEPT ORTHOPED SURG/TOKYO//JAPAN/
Journal: ENDOCRINOLOGY, 1997, V138, N11 (NOV), P4959-4965
ISSN: 0013-7227 Publication date: 19971100
Publisher: ENDOCRINE SOC, 4350 EAST WEST HIGHWAY SUITE 500, BETHESDA, MD 20814-4110
Language: English Document Type: ARTICLE
Abstract: Interleukin (IL)-6, IL -11 , leukemia inhibitory factor, and oncostatin M similarly induce osteoclast formation in cocultures of osteoblastic cells and bone marrow cells. These cytokines share a common signal transducer, gp130, which forms a receptor complex with the specific receptor for each cytokine. To investigate the role of gp130 in osteoclast development, we examined bone tissues in gp130-deficient and wild-type newborn mice of the ICR background. Soft x-ray radiographs and microfocus x-ray computed tomographs revealed that bone marrow cavities were present in tibiae and radii of both wildtype and gp130-deficient mice. Microfocus x-ray computed tomography and histological examination demonstrated a decrease in the amount of trabeculae at the metaphysial region in tibiae and radii of the gp130-deficient mice compared with the wild-type mice. The number of osteoclasts in gp130-deficient mice was about double that in the wild-type mice. There were no apparent differences in the distributions of alkaline phosphatase-positive osteoblasts and the osteoid surface on the trabecular bone at the metaphysial region between the wild-type and gp130-deficient mice. The volume of mineralized trabecular bones was also decreased at mandibulae, accompanied by the increased number of osteoclasts in gp130-deficient mice compared with the wild-type and heterozygous mice. These results suggest that the formation of osteoclasts is not solely dependent on gp130 signaling, at least during fetal development. The osteoclastic bone resorption in gp130-deficient mice may be caused by the functional redundancy of bone -resorbing hormones and cytokines other than those of the IL-6 family.

4/AB/12 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05858040 Genuine Article#: XC376 Number of References: 48
Title: The synovial expression and serum levels of interleukin-6, interleukin- 11, leukemia inhibitory factor, and oncostatin M in rheumatoid arthritis (ABSTRACT AVAILABLE)
Author(s): Okamoto H; Yamamura M (REPRINT) ; Morita Y; Harada S; Makino H; Ota Z
Corporate Source: OKAYAMA UNIV,SCH MED, DEPT MED 3, 2-5-1 SHIKATA CHO/OKAYAMA 700//JAPAN/ (REPRINT); OKAYAMA UNIV,SCH MED, DEPT MED 3/OKAYAMA 700//JAPAN/
Journal: ARTHRITIS AND RHEUMATISM, 1997, V40, N6 (JUN), P1096-1105
ISSN: 0004-3591 Publication date: 19970600
Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106
Language: English Document Type: ARTICLE
Abstract: Objective, To determine the expression of interleukin-6 (IL-6), IL -11 , leukemia inhibitory factor (LIF), and oncostatin M (OSM) and their major cellular sources in the joints of rheumatoid arthritis (RA) patients, as well as the correlation of circulating levels of these IL-6-type cytokines and C-reactive protein (CRP).

Methods. Messenger RNA (mRNA) and protein levels for IL-6, IL -11 , LIF, and OSM were determined by using reverse transcription-polymerase chain reaction and enzyme-linked immunosorbent assay, respectively.

Results. Cells isolated from the synovium of RA patients expressed mRNA for IL-6, IL -11 , LIF, and OSM at higher levels than did synovial cells from osteoarthritis (OA) patients, and spontaneously released greater quantities of these proteins in culture, Fibroblast cell lines derived from Ri synovium were able to produce IL-6, IL -11 , and LIF, but not OSM, when stimulated with IL-1 and tumor necrosis factor alpha. OSM was found to be produced spontaneously by synovial tissue macrophages. IL-6, IL -11 , LIF, and OSM were present in synovial fluid from the RA patients; levels of IL-6, LIF, and OSM were present in significantly greater quantities in RA patients than in OA patients, However, only IL-6 was significantly elevated in the serum of RA patients and correlated with the serum CRP level, while other IL-6-type cytokines were not detected.

Conclusions. IL-6, IL -11 , LIF, and OSM are all produced in large amounts at the site of disease activity, but IL-6 derived from synovial fibroblasts may be the major hormone-like mediator that induces the hepatic synthesis of acute-phase proteins in RA.

4/AB/13 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05831960 Genuine Article#: XA471 Number of References: 31
Title: Involvement of different second messengers in parathyroid hormone- and interleukin-1-induced interleukin-6 and interleukin- 11 production in human bone marrow stromal cells (ABSTRACT AVAILABLE)
Author(s): Kim GS (REPRINT) ; Kim CH; Choi CS; Park JY; Lee KU
Corporate Source: UNIV ULSAN,COLL MED, ASAN MED CTR, DIV ENDOCRINOL, POB 145/SEOUL 138600//SOUTH KOREA/ (REPRINT)

Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1997, V12, N6 (JUN), P 896-902
ISSN: 0884-0431 Publication date: 19970600
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148
Language: English Document Type: ARTICLE
Abstract: Previous studies have suggested that increased secretion of bone active cytokines, such as interleukin-6 (IL-6) and interleukin -11 (IL -11), from osteoblasts and stromal cells play a pivotal role in the activation of osteoclasts and the genesis of osteoporosis , Various systemic and local factors can stimulate IL-6/IL -11 production, but the intracellular mechanism for such stimulation is largely unknown. In this study, we characterized the second messenger signaling in parathyroid hormone (PTH)- and IL-1-induced production of IL-6/IL -11 and studied the possible modulating effects of estrogen, rhPTH(1-34) and rhIL-1 alpha: dose-dependently stimulated IL-6 and IL -11 production from human bone marrow stromal cells (hBMSCs), Agonists for protein kinase A (PKA) (forskolin), and protein kinase C (PKC) (phorbol 12-myristate 13-acetate; PMA) also stimulated IL-6/IL -11 production. Rp-diastereoisomer of adenosine cyclic 3',5'-phosphorothioate (Rp-cAMPS) and H-8, inhibitors of PKA, significantly inhibited PTH-stimulated IL-6/IL -11 production, but did not inhibit IL-1-stimulated IL-6/IL -11 production, In contrast, staurosporine and calphostin C, inhibitors of PKC, suppressed IL-1-stimulated, but not PTH stimulated, IL-6/IL -11 production, Pretreatment of cells with 17 beta-estradiol (17 beta-E-2) antagonized IL-1-stimulated IL-6 production, However, PTH-stimulated IL-6 production and IL-1- and PTH-stimulated IL -11 production were not affected by 17 beta-E-2. Similarly, 17 beta-E-2 inhibited PMA-stimulated IL-6 production, whereas neither forskolin-stimulated IL-6/IL -11 production nor PMA-stimulated IL -11 production was affected by 17 beta-E-2. These results indicate that different second messengers are involved in PTH- and IL-1-induced IL-6 and IL -11 production by hBMSCs: PTH and IL-1 stimulate IL-6/IL -11 production via a PKA-dependent and PKC dependent pathway, respectively. Furthermore, our results suggest that regulation of cytokine production by estrogen in hBMSCs is selective; only the IL-1-induced IL-6 production, which is mediated by PKC pathway, is inhibited, but PTH-induced IL-6 production and PTH/IL-1-induced IL -11 production are not inhibited by estrogen.

4/AB/14 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05816936 Genuine Article#: WZ565 Number of References: 23
Title: Isolation of a novel cytokine from human fibroblasts that specifically inhibits osteoclastogenesis (ABSTRACT AVAILABLE)
Author(s): Tsuda E (REPRINT) ; Goto M; Mochizuki S; Yano K; Kobayashi F; Morinaga T; Higashio K
Corporate Source: SNOW BRAND MILK PROD CO LTD,LIFE SCI RES INST/ISHIBASHI/TOCHIGI 32905/JAPAN/ (REPRINT)
Journal: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, 1997, V234, N1 (MAY 8), P137-142
ISSN: 0006-291X Publication date: 19970508
Publisher: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
Language: English Document Type: ARTICLE
Abstract: A factor which inhibits osteoclast -like cell formation was found in the conditioned medium of human embryonic lung fibroblasts, IMR-90. The factor, termed osteoclastogenesis inhibitory factor,

OCIF, was purified to homogeneity. OCIF is a heparin-binding basic glycoprotein and has been isolated as a monomer with an apparent molecular weight (Mr) of 60,000 and a homodimer with a Mr of 120,000. The N-terminus of OCIF is blocked and the determination of internal amino acid sequences revealed that OCIF has no homology to known proteins. OCIF inhibited in a dose-dependent manner osteoclastogenesis elicited through three distinct signaling pathways stimulated by 1 alpha,25-dihydroxy vitamin D-3, parathyroid hormone, and interleukin - 11 , respectively, in a dose range of 1 to 40 ng/ml (IC50 = 4 to 6 ng/ml). OCIF neither inhibits bone resorption by mature osteoclasts nor exerts any other biological activities. These data strongly suggest that OCIF is a novel cytokine which specifically inhibits osteoclastogenesis . (C) 1997 Academic Press.

4/AB/15 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05783711 Genuine Article#: WW911 Number of References: 30
Title: Stimulation of interleukin- 11 production from osteoblast-like cells by transforming growth factor-beta and tumor cell factors (ABSTRACT AVAILABLE)
Author(s): Morinaga Y; Fujita N; Ohishi K; Tsuruo T (REPRINT)
Corporate Source: UNIV TOKYO,INST MOL & CELLULAR BIOSCI, BUNKYO KU, 1-1-1 YAYOI/TOKYO 113//JAPAN/ (REPRINT); UNIV TOKYO,INST MOL & CELLULAR BIOSCI, BUNKYO KU/TOKYO 113//JAPAN/; JAPANESE FDN CANC RES,CTR CANC CHEMOTHERAPY/TOKYO 170//JAPAN/
Journal: INTERNATIONAL JOURNAL OF CANCER, 1997, V71, N3 (MAY 2), P422-428
ISSN: 0020-7136 Publication date: 19970502
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605 THIRD AVE, NEW YORK, NY 10158-0012
Language: English Document Type: ARTICLE
Abstract: Bone is one of the most common sites of metastasis in melanoma and breast cancer cells. Human melanoma (A375M) and human breast cancer (MDA-MB-231) cells form osteolytic bone metastasis in vivo when these tumor cells are injected into the left ventricles of BALB/c nude mice. These tumor cells promote bone resorption in the in vitro neonatal murine calvaria organ culture system by indirectly stimulating the production of a bone resorption-inducing factor (or factors) from human osteoblast -like cells. This secreted factor was identified as interleukin -11 (IL -11). Although many cytokines and hormones were associated with IL -11 production from osteoblasts , transforming growth factor-beta (TGF-beta) was found to be involved in the promotion of IL -11 production from osteoblasts , because the addition of a neutralizing anti-TGF-beta antibody decreased the production of IL -11 . However, these tumor cells did not produce TGF-beta by themselves. We found that they enhanced IL -11 production by activating latent TGF-beta produced from osteoblast -like cells. Our results indicate that metastatic tumor cells induce osteolysis by activating TGF-beta, which leads IL -11 production from osteoblasts to promote bone resorption. (C) 1997 Wiley-Liss, Inc.

4/AB/16 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05725939 Genuine Article#: WT776 Number of References: 28
Title: Interleukin-6 receptor antagonists inhibit interleukin- 11

biological activity (ABSTRACT AVAILABLE)
Author(s): Sun RX; Gennaro C; Rocco S; Gu ZJ; Klein B (REPRINT)
Corporate Source: CNRS,INST MOL GENET, 1919 ROUTE MENDE/F-34033 MONTPELLIER//FRANCE/ (REPRINT); CNRS,INST MOL GENET/F-34033 MONTPELLIER//FRANCE/; HOP ST ELOI,UNIT CELLULAR THERAPY/F-34000 MONTPELLIER//FRANCE/; IRBM,/I-0040 POMEZIA/ROME/ITALY/
Journal: EUROPEAN CYTOKINE NETWORK, 1997, V8, N1 (MAR), P51-56
ISSN: 1148-5493 Publication date: 19970300
Publisher: JOHN LIBBEY EUROTEXT LTD, 127 AVE DE LA REPUBLIQUE, 92120 MONTROUGE, FRANCE
Language: English Document Type: ARTICLE
Abstract: The IL-6 receptor system comprises two functionally different chains: a binding chain (IL-6R) and a signal-transducing chain (gp130). The IL-6/IL-6R complexes associate with gp130, induce its dimerization and signal transduction. When IL-6 is complexed to IL-6R, two distinct sites of IL-6 are able to bind gp130. Other cytokines - oncostatin M (OM), leukemia inhibitory factor (LIF) or ciliary neurotrophic factor (CNTF) also use the gp130 transducer and induce its heterodimerization with LIF receptor (LIFR). A series of IL-6 mutants have been generated which function as IL-6 receptor antagonists (IL-6RA). These IL-6RA carried substitutions that increased their affinity with IL-6R and abolished 1 or the 2 sites of interaction with gp130. All the IL-6RA inhibited wild-type IL-6. The IL-6RA with one mutated binding site to gp130 inhibited IL -11 activity. They did not affect those of CNTF, LIF and OM, even when used at a very high concentration at which virtually all membrane IL-6R were bound to IL-6RA, IL-6RA with two mutated gp130 binding sites did not affect IL -11 , CNTF, LIF or OM activities. The results indicate that the interaction of one gp130 chain with IL-6R/IL-6R complexes inhibited further the dimerization of gp130 induced by IL -11 /IL -11R but not its heterodimerization with LIFR. Thus these IL-6RA can also function as IL -11 antagonists.

4/AB/17 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05650263 Genuine Article#: WN148 Number of References: 54
Title: Advanced glycation endproducts stimulate interleukin-6 production by human bone-derived cells (ABSTRACT AVAILABLE)
Author(s): Takagi M; Kasayama S (REPRINT) ; Yamamoto T; Motomura T; Hashimoto K; Yamamoto H; Sato B; Okada S; Kishimoto T
Corporate Source: OSAKA UNIV,SCH MED, DEPT MED 3, 2-2 YAMADAOKA/SUITA/OSAKA 565/JAPAN/ (REPRINT); OSAKA UNIV,SCH MED, DEPT MED 3/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH MED, DEPT PEDIAT/SUITA/OSAKA 565/JAPAN/; NISSEI HOSP,DEPT MED 3/OSAKA//JAPAN/
Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1997, V12, N3 (MAR), P 439-446
ISSN: 0884-0431 Publication date: 19970300
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148
Language: English Document Type: ARTICLE
Abstract: Advanced glycation endproducts (AGEs), which result from nonenzymatic reactions of glucose,vith tissue proteins, have been shown to accumulate on long-lived proteins in advanced aging and diabetes mellitus, Thus, AGEs have been implicated in some of the chronic complications associated with these disorders, In this study, we investigated the effects of the glucose-modified protein on the production of the potent bone resorption factors by cells derived from explants of human bone . AGEs stimulated the release of interleukin-6 (IL-6) in the culture supernatants from the bone

-derived cells and increased the levels of IL-6 mRNA in the cells, By contrast, the levels of IL -11 in the culture supernatants were not altered by AGEs, and the other bone resorption factors IL-1 alpha and IL-1 beta were undetectable (<1.0 pg/ml) either without or with the treatment of AGEs. Electrophoretic mobility-shift assays revealed that the transcription nuclear factor-KB, which is critical for the inducible expression of IL-6, was activated in the nuclear extracts from mouse osteoblastic MC3T31-E1 cells treated with AGEs. These results suggest that AGEs are involved in bone remodeling modulation by stimulating IL-6 production in human bone -derived cells.

4/AB/18 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

05087122 Genuine Article#: TP538 Number of References: 168
Title: IL-6 CYTOKINE FAMILY AND SIGNAL-TRANSDUCTION - A MODEL OF THE CYTOKINE SYSTEM (Abstract Available)
Author(s): HIBI M; NAKAJIMA K; HIRANO T
Corporate Source: OSAKA UNIV,SCH MED,BIOMED RES CTR,2-2 YAMADAOKA/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH MED,BIOMED RES CTR/SUITA/OSAKA 565/JAPAN/
Journal: JOURNAL OF MOLECULAR MEDICINE-JMM, 1996, V74, N1 (JAN), P1-12
ISSN: 0946-2716
Language: ENGLISH Document Type: REVIEW
Abstract: The interleukin 6 (IL-6) cytokine family, which includes IL-6, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), IL -11 and cardiotrophin-1 (CT-1), exhibits pleiotropy and redundancy in biological. activities. The IL-6 family cytokines exhibit a helical structure. Their receptors belong to the type 1 cytokine receptor family. The receptors of the IL-6 family cytokines share a receptor subunit, which explains one of the mechanisms of functional redundancy. In this review, we describe the general features of the IL-6 cytokine family and its signal transduction mechanisms. Many functional properties of the IL-6 family of cytokines and their receptors are general features of the cytokine system.

4/AB/19 (Item 11 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04967519 Genuine Article#: UV819 Number of References: 51
Title: ONCOSTATIN-M (OSM) STIMULATES RESORPTION AND INHIBITS SYNTHESIS OF PROTEOGLYCAN IN PORCINE ARTICULAR-CARTILAGE EXPLANTS (Abstract Available)
Author(s): HUI W; BELL M; CARROLL G
Corporate Source: ROYAL PERTH HOSP,DEPT RHEUMAT DIS/PERTH/WA/AUSTRALIA/; ROYAL PERTH HOSP,DEPT RHEUMAT DIS/PERTH/WA/AUSTRALIA/; ROYAL PERTH HOSP,RES CTR/PERTH/WA/AUSTRALIA/
Journal: CYTOKINE, 1996, V8, N6 (JUN), P495-500
ISSN: 1043-4666
Language: ENGLISH Document Type: ARTICLE
Abstract: Oncostatin M (OSM) is structurally and functionally similar to leukaemia inhibitory factor (LIF), interleukin 6 (IL-6), interleukin 11 (IL -11) and ciliary neurotrophic factor (CNTF). We have previously shown that LIF stimulates proteoglycan release and suppresses proteoglycan synthesis in pig and goat cartilage explants. The aim of this study was to determine whether OSM and related

cytokines influence proteoglycan metabolism in pig cartilage explants. Slices of pig articluar cartilage were incubated for 6 days in serum free DMEM with or without cytokines. The total proteoglycan content in papain digested cartilage explants and medium was determined by the 1,9 dimethylmethylene blue method. Cytokine activity was assessed by determining the percentage release of total proteoglycan. To evaluate proteoglycan synthesis, cartilage was cultured for 48 h under the same conditions and in the final 6 h the tissue was cultured in sulphate free DMEM containing (SO4)-S-35. The radioactivity in the medium and tissue was determined in cetylpyridinium chloride precipitates. Biosynthetic activity was expressed as DPM per mg wet weight of cartilage. Dose dependent stimulation of proteoglycan release and suppression of proteoglycan synthesis were observed with rhOSM. IL-6, IL -11 and CNTF also inhibited proteoglycan synthesis in a dose dependent manner but the degree of inhibition was less than that for OSM and these cytokines had no significant effect on proteoglycan release. New biological effects have been identified for OSM and the related cytokines CNTF and IL -11 . All three of these cytokines, like LIF and IL-6, suppress proteoglycan synthesis in pig cartilage explants. This common effect suggests that the gp130 subunit of the receptors for these cytokines may represent a common signalling pathway whereby proteoglycan synthesis is regulated, Whilst OSM and LIF stimulate proteoglycan catabolism; IL-6 IL -11 and OSM do not. Thus these effects are not always coupled and activation of gp130 alone may not be a sufficient signal for proteoglycan catabolism. (C) 1996 Academic Press Limited

4/AB/20 (Item 12 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04634175 Genuine Article#: TY261 Number of References: 65
Title: INTERLEUKIN-4 INHIBITS PROSTAGLANDIN-G H-SYNTHASE-2 AND CYTOSOLIC PHOSPHOLIPASE A(2) INDUCTION IN NEONATAL PARIETAL BONE CULTURES (Abstract Available)
Author(s): KAWAGUCHI H; NEMOTO K; RAISZ LG; HARRISON JR; VOZNESENSKY OS; ALANDER CB; PILBEAM CC
Corporate Source: UNIV CONNECTICUT,CTR HLTH,DEPT MED,DIV ENDOCRINOL & METAB,236 FARMINGTON AVE/FARMINGTON//CT/06030; UNIV CONNECTICUT,CTR HLTH,DEPT MED,DIV ENDOCRINOL & METAB/FARMINGTON//CT/06030
Journal: JOURNAL OF BONE AND MINERAL RESEARCH, 1996, V11, N3 (MAR), P 358-366
ISSN: 0884-0431
Language: ENGLISH Document Type: ARTICLE
Abstract: We have shown previously that prostaglandin (PG) production in 7-day-old neonatal mouse calvarial cultures is regulated largely by changes in prostaglandin G/H synthase-2 (PGHS-2) expression and to a lesser extent by changes in arachidonic acid (AA) release, In this study, we examined the effects of interleukin-4 (IL-4), and its interactions with other cytokines and with parathyroid hormone (PTH), on mRNA levels of PGHS-2, PGHS-1, and cytosolic phospholipase A(2) (cPLA(2)) and on medium protaglandin E(2) (PGE(2)) levels in calvarial cultures, IL-1 and tumor necrosis factor-alpha (TNF-alpha), both at 1-100 ng/ml, and PTH at 0.1-10 nM increased PGHS-2 and cPLA(2) mRNA and medium PGE(2) levels dose-dependently after 4 h of treatment, IL-6 and IL -11 at 1-100 ng/ml did not affect mRNA or PGE(2) levels, IL-4 at 1-100 ng/ml decreased PGHS-2 and cPLA(2) mRNA and PGE(2) levels in control as well as IL-1, TNF-alpha, and PTH-stimulated cultures, The inhibition of PGHS-2 and cPLA(2) mRNA expression by IL-4 (10 ng/ml) was present at 1 h, reached a maximum at 4 h, and persisted for 24 h, The

effects were maintained in the presence of cycloheximide. IL-4 also decreased PGHS-2 protein levels in control and IL-1-stimulated cultures, PGHS-1 mRNA levels were not stimulated by any of the factors studied nor inhibited by IL-4. IL-4 partially inhibited control and PTH-stimulated Ca-45 release from prelabeled mouse calvariae at 4 days, However, neither the inhibition of resorption by IL-4 nor the stimulation by IL-1 and PTH were altered by indomethacin (1 mu M). We conclude that (1) IL-1, TNF-alpha, and PTH, but not IL-6 nor IL -11 , can increase the expression of PGHS-2, cPLA(2), and PGE(2) production in cultured mouse calvariae; (2) IL-4 inhibits PGE(2) production in both control and stimulated calvarial cultures by inhibiting PGHS-2 and cPLA(2); and (3) IL-4 has an inhibitory effect on bone resorption which is independent of PG production.

4/AB/21 (Item 13 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04627818 Genuine Article#: TX603 Number of References: 32
Title: CYTOKINE EXPRESSION BY HUMAN MARROW-DERIVED MESENCHYMAL PROGENITOR CELLS IN-VITRO - EFFECTS OF DEXAMETHASONE AND IL-1-ALPHA (Abstract Available)
Author(s): HAYNESWORTH SE; BABER MA; CAPLAN AI
Corporate Source: CASE WESTERN RESERVE UNIV,SKELETAL RES CTR,DEPTBIOL,2080 ADELBERT RD/CLEVELAND//OH/44106
Journal: JOURNAL OF CELLULAR PHYSIOLOGY, 1996, V166, N3 (MAR), P585-592
ISSN: 0021-9541
Language: ENGLISH Document Type: ARTICLE
Abstract: We previously reported the purification, culture-expansion, and osteogenic differ entiation potential of mesenchymal progenitor cells (MPCs) derived from human bone marrow. As a first step to establishing the phenotypic characteristics of MPCs, we reported on the identification of unique cell surface proteins which were detected with monoclonal antibodies. In this study, the phenotypic characterization of human marrow-derived MPCs is further established through the identification of a cytokine expression profile under standardized growth medium conditions and in the presence of regulators of the osteogenic and stromal cell lineages, dexamethasone and interleukin-1 alpha (IL-1 alpha), respectively. Constitutively expressed cytokines in this growth phase include G-CSF, SCF, LIF, M-CSF, IL-6, and IL -11 , while CM-CSF, IL-3, TGF-beta 2, and OSM were not detected in the growth medium. Exposure of cells in growth medium to dexamethasone resulted in a decrease in the expression of LIF, IL-6, and IL -11 . These cytokines have been reported to exert influence on the differentiation of cells derived from the bone marrow stroma through target cell receptors that utilize gp130-associated signal transduction pathways. Dexamethasone had no effect on the other cytokines expressed under growth medium conditions and was not observed to increase the expression of any of the cytokines measured in this study. In contrast, IL-1 alpha increased the expression of G-CSF, M-CSF, LIF, IL-6, and IL -11 and induced the expression of GM-CSF. IL-1 alpha had no effect on SCF expression and was not observed to decrease the production of any of the cytokines assayed. These data indicate that MPCs exhibit a distinct cytokine expression profile. We interpret this cytokine profile to suggest that MPCs serve specific supportive functions in the microenvironment of bone marrow. MPCs provide inductive and regulatory information which are consistent with the ability to support hematopoiesis, and also supply autocrine, paracrine, and juxtacrine factors that influence the cells of the marrow microenvironment itself. In addition, the cytokine profiles expressed by MPCs, in response to

dexamethasone and IL-1 alpha, identify specific cytokines whose levels of expression change as MPCs differentiate or modulate their phenotype during osteogenic or stromagenic lineage entrance/progression. (C) 1996 Wiley-Liss, Inc.

4/AB/22 (Item 14 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04548672 Genuine Article#: TR380 Number of References: 48
Title: DETECTION OF RECEPTORS FOR INTERLEUKIN-6, INTERLEUKIN- 11, LEUKEMIA INHIBITORY FACTOR, ONCOSTATIN-M, AND CILIARY NEUROTROPHIC FACTOR IN BONE-MARROW STROMAL OSTEOBLASTIC CELLS (Abstract Available)
Author(s): BELLIDO T; STAHL N; FARRUGGELLA TJ; BORBA V; YANCOPOULOS GD; MANOLAGAS SC
Corporate Source: UNIV ARKANSAS MED SCI HOSP,DIV ENDOCRINOL & METAB,4301 W MARKHAM,MAIL SLOT 587/LITTLE ROCK//AR/72205; UNIV ARKANSAS MED SCI HOSP,CTR OSTEOPOROSIS & METAB BONE DIS/LITTLE ROCK//AR/72205; JOHN L MCCLELLAN MEM VET ADM MED CTR,GRECC/LITTLE ROCK//AR/72205; REGENERON PHARMACEUT INC/TARRYTOWN//NY/10591
Journal: JOURNAL OF CLINICAL INVESTIGATION, 1996, V97, N2 (JAN 15), P 431-437
ISSN: 0021-9738
Language: ENGLISH Document Type: ARTICLE
Abstract: The functional receptor complexes assembled in response to interleukin-6 and -11 (IL-6 and IL -11), leukemia inhibitory factor (LIF), oncostatin M (OSM), and ciliary neurotrophic factor (CNTF), all involve the signal transducer gp130: IL-6 and IL -11 induce homodimerization of gp130, while the rest heterodimerize gp130 with other gp130-related beta subunits, Some of these cytokines (IL-6, IL -11 , and CNTF) also require a specificity-determining alpha subunit not directly involved in signaling. We have searched for functional receptor complexes for these cytokines in cells of the bone marrow stromal/osteoblastic lineage, using tyrosine phosphorylation of the beta subunits as a detection assay. Collectively, murine calvaria cells, bone marrow-derived murine cell lines (+/+LDA11 and MBA13.2), as well as murine (MC3T3-E1) and human (MG-63) osteoblast -like cell lines displayed all the previously recognized alpha and beta subunits of this family of receptors. However, individual cell types had different constellations of alpha and beta subunits, In addition and in difference to the other cell types examined, MC3T3-E1 cells expressed a heretofore unrecognized form of gp130; and MG-63 displayed an alternative form (type II) of the OSM receptor. These findings establish that stromal/osteoblastic cells are targets for the actions of all the members of the cytokine subfamily that shares the gp130 signal transducer; and suggest that different receptor repertoires may be expressed at different stages of differentiation of this lineage.

4/AB/23 (Item 15 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04411515 Genuine Article#: TB894 Number of References: 64
Title: INTERLEUKIN (IL)-6 INDUCTION OF OSTEOCLAST DIFFERENTIATION DEPENDS ON IL-6 RECEPTORS EXPRESSED ON OSTEOBLASTIC CELLS BUT NOT ON OSTEOCLAST PROGENITORS (Abstract Available)
Author(s): UDAGAWA N; TAKAHASHI N; KATAGIRI T; TAMURA T; WADA S; FINDLAY DM ; MARTIN TJ; HIROTA H; TADA T; KISHIMOTO T; SUDA T

Corporate Source: SHOWA UNIV,SCH DENT,DEPT BIOCHEM,SHINAGAWA KU,1-5-8 HATANODAI/TOKYO 142//JAPAN/; SHOWA UNIV,SCH DENT,DEPT BIOCHEM,SHINAGAWA KU/TOKYO 142//JAPAN/; UNIV MELBOURNE,ST VINCENTS INST MED RES/FITZROY/VIC 3065/AUSTRALIA/; OSAKA UNIV,SCH MED,DEPT MED 3/OSAKA 565//JAPAN/; OSAKA UNIV,INST MOLEC & CELL BIOL/OSAKA 565//JAPAN/
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 1995, V182, N5 (NOV 1), P 1461-1468
ISSN: 0022-1007
Language: ENGLISH Document Type: ARTICLE
Abstract: We reported that interleukin (IL) 6 alone cannot induce osteoclast formation in cocultures of mouse bone marrow and osteoblastic cells, but soluble IL-6 receptor (IL-6R) strikingly triggered osteoclast formation induced by IL-6. In this study, we examined the mechanism of osteoclast formation by IL-6 and related cytokines through the interaction between osteoblastic cells and osteoclast progenitors. When dexamethasone was added to the cocultures, IL-6 could stimulate osteoclast formation without the help of soluble IL-6R. Osteoblastic cells expressed a very low level of IL-6R mRNA, whereas fresh mouse spleen and bone marrow cells, both of which are considered to be osteoclast progenitors, constitutively expressed relatively high levels of IL-6R mRNA. Treatment of osteoblastic cells with dexamethasone induced a marked increase in the expression of IL-6R mRNA. By immunoblotting with antiphosphotyrosine antibody, IL-6 did not tyrosine-phosphorylate a protein with a molecular mass of 130 kD in osteoblastic cells but did so in dexamethasone-pretreated osteoblastic cells. Osteoblastic cells from transgenic mice constitutively expressing human IL-6R could support osteoclast development in the presence of human IL-6 alone in cocultures with normal spleen cells. In contrast, osteoclast progenitors in spleen cells from transgenic mice overexpressing human IL-6R were not able to differentiate into osteoclasts in response to IL-6 in cocultures with normal osteoblastic cells. These results clearly indicate that the ability of IL-6 to induce osteoclast differentiation depends on signal transduction mediated by IL-6R expressed on osteoblastic cells but not on osteoclast progenitors.

4/AB/24 (Item 16 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

04319819 Genuine Article#: RU724 Number of References: 30
Title: MODULATION OF OSTEOCLAST DIFFERENTIATION BY LOCAL FACTORS (Abstract Available)
Author(s): SUDA T; UDAGAWA N; NAKAMURA I; MIYAURA C; TAKAHASHI N
Corporate Source: SHOWA UNIV,SCH DENT,DEPT BIOCHEM,SHINAGAWA KU,1-5-8 HATANODAI/TOKYO 142//JAPAN/
Journal: BONE, 1995, V17, N2 (AUG), PS87-S91
ISSN: 8756-3282
Language: ENGLISH Document Type: ARTICLE
Abstract: Bone -resorbing osteoclasts are of hemopoietic cell origin, probably of the CFU-M-derived monocyte-macrophage family, Bone marrow-derived osteoblastic stromal cells play an important role in modulating the differentiation of osteoclast progenitors in two different ways: one is the production of soluble factors, and the other is cell-to-cell recognition between osteoclast progenitors and osteoblastic stromal cells, M-CSF is probably the most important soluble factor, which appears to be necessary for not only proliferation of osteoclast progenitors, but also differentiation into mature osteoclasts and their survival, A number of local factors as well as systemic hormones induce osteoclast differentiation. They

are classified into three categories in terms of the signal transduction: vitamin D receptor-mediated signals [1 alpha,25(OH)(2)D-3] protein kinase A-mediated signals (PTH, PTHrP, PGE(2), and IL-1); and gp130-mediated signals (IL-6, IL -11 , oncostatin M, and leukemia inhibitory factor), All of these osteoclast -inducing factors appear to act on osteoblastic cells to commonly induce osteoclast differentiation factor (ODF), which recognizes osteoclast progenitors and prepares them to differentiate into mature osteoclasts . This line of approach will undoubtedly produce new ways to treat several metabolic bone diseases caused by abnormal osteoclast recruitment such as osteoporosis , osteopetrosis , Paget's disease, rheumatoid arthritis, and periodontal disease.

4/AB/25 (Item 17 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

04319814 Genuine Article#: RU724 Number of References: 45
Title: ROLE OF CYTOKINES IN BONE-RESORPTION (Abstract Available)
Author(s): MANOLAGAS SC
Corporate Source: UNIV ARKANSAS MED SCI HOSP,MCCLELLAN VET ADM CTR,GRECC,4301 W MARKHAM,MAIL SLOT 587/LITTLE ROCK//AR/72205; UNIV ARKANSAS MED SCI HOSP,CTR OSTEPOROSIS & METAB BONE DIS,DIV ENDOCRINOL & METAB/LITTLE ROCK//AR/72205
Journal: BONE, 1995, V17, N2 (AUG), PS63-S67
ISSN: 8756-3282
Language: ENGLISH Document Type: ARTICLE
Abstract: It has been established during the past few years that interleukin(s)-1, -6, -11 (IL-I, IL-6, IL -11), and tumor necrosis factor (TNF) can stimulate osteoclast development and thereby the process of bone resorption, Moreover, upregulation of the production and/or action of IL-6 has been implicated in the pathogenesis of disease states characterized by excessive osteoclastic bone resorption, including the osteopenias associated with loss of either ovarian or testicular function, This article highlights this evidence and attempts to clarify the role of cytokines in the bone loss associated with gonadal deficiency, Specifically, it reviews data demonstrating that the protective effects of estrogens and androgens on the skeleton are mediated through their ability to inhibit IL-6 production, Both of these steroids exert their effects by inhibiting the transcriptional activity of the IL-6 gene promoter via mechanisms involving their respective specific receptors, Upon loss of gonadal function in either sex, there occurs an upregulation of osteoclast formation which is mediated by IL-6, Consistent with this, IL-6 deficient mice do not exhibit an increase in the formation of osteoclasts after ovariectomy or orchidectomy, and are protected from the bone loss caused by the loss of gonadal function in either sex, Even though these observations establish that IL-6 is an essential pathogenetic factor in the bone loss caused by gonadal deficiency, it remains unclear whether IL-6 is the sole pathogenetic factor or whether IL-1, TNF, and IL -11 may also be involved, However, in contrast to IL-6, these cytokines do not seem to be directly regulated by sex steroids, Therefore, it is unlikely that they are causative factors in the pathogenesis of this condition; yet, because they are required for osteoclast development, they may be participatory factors in the bone loss caused by gonadal deficiency.

4/AB/26 (Item 18 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

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04195272 Genuine Article#: RN467 Number of References: 116
Title: INTERLEUKIN-6 FAMILY OF CYTOKINES AND GP130
Author(s): KISHIMOTO T; AKIRA S; NARAZAKI M; TAGA T
Corporate Source: OSAKA UNIV,SCH MED,DEPT MED 3,2-2 YAMADAOKA/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,INST MOLEC & CELLULAR BIOL/SUITA/OSAKA 565/JAPAN/
Journal: BLOOD, 1995, V86, N4 (AUG 15), P1243-1254
ISSN: 0006-4971
Language: ENGLISH Document Type: REVIEW

4/AB/27 (Item 19 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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04150239 Genuine Article#: RH894 Number of References: 61
Title: OVARIECTOMY ENHANCES AND ESTROGEN REPLACEMENT INHIBITS THE ACTIVITY OF BONE-MARROW FACTORS THAT STIMULATE PROSTAGLANDIN PRODUCTION IN CULTURED MOUSE CALVARIAE (Abstract Available)
Author(s): KAWAGUCHI H; PILBEAM CC; VARGAS SJ; MORSE EE; LORENZO JA; RAISZ LG
Corporate Source: UNIV CONNECTICUT,CTR HLTH,DEPT MED,DIV ENDOCRINOL & METAB/FARMINGTON//CT/06030; UNIV CONNECTICUT,CTR HLTH,DEPT MED,DIV ENDOCRINOL & METAB/FARMINGTON//CT/06030; UNIV CONNECTICUT,CTR HLTH,DEPT LAB MED,DIV HEMATOL BLOOD BANK/FARMINGTON//CT/06030; DEPT VET AFFAIRS MED CTR,DEPT MED/NEWINGTON//CT/06111
Journal: JOURNAL OF CLINICAL INVESTIGATION, 1995, V96, N1 (JUL), P539-548
ISSN: 0021-9738
Language: ENGLISH Document Type: ARTICLE
Abstract: To examine PG production in estrogen deficiency, we studied effects on cultured neonatal mouse calvariae of bone marrow supernatants (MSup) from sham-operated (SHAM), ovariectomized (OVX), or 17 beta-estradiol (OVX+E)-treated mice, MSups were obtained 3 wk after OVX when bone density had decreased significantly, 10-60% MSup increased medium PGE(2) and levels of mRNA for inducible and constitutive prostaglandin G/H synthase (PGHS-2 and PGHS-1) and cytosolic phospholipase A(2) in calvarial cultures. OVX MSups had twofold greater effects on PGHS-2 and medium PGE(2) than other MSups, IL-1 receptor antagonist and anti-IL-1 alpha neutralizing antibody decreased MSup-stimulated PGHS-2 mRNA and PGE(2) levels and diminished differences among OVX, sham-operated, and OVX+E groups, In contrast, antibodies to IL-1 beta, IL-6, IL -11 , and TNF alpha had little effect. There were no significant differences in IL-1 alpha concentrations or IL-1 alpha mRNA levels in MSups or marrow cells, PGHS-2 mRNA in freshly isolated tibiae from OVX mice was slightly greater than from sham-operated. We conclude that bane marrow factors can increase PG production through stimulation of PGHS-2; that OVX increases and estrogen decreases activity of these factors; and that IL-1 alpha activity, together with additional unknown factors, mediates the differential MSup effects.

4/AB/28 (Item 20 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03975404 Genuine Article#: QW230 Number of References: 49
Title: NEW INSIGHTS INTO THE CELLULAR, BIOCHEMICAL, AND MOLECULAR-BASIS OF POSTMENOPAUSAL AND SENILE OSTEOPOROSIS - ROLES OF IL-6 AND GP130 (

Abstract Available)
Author(s): MANOLAGAS SC; BELLIDO T; JILKA RL
Corporate Source: UNIV ARKANSAS MED SCI HOSP,DIV ENDOCRINOL & METAB,4301 W MARKHAM/LITTLE ROCK//AR/72205; UNIV ARKANSAS MED SCI HOSP,CTR OSTEOPOROSIS & METAB BONE DIS/LITTLE ROCK//AR/72205
Journal: INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, 1995, V17, N2 (FEB), P109-116
ISSN: 0192-0561
Language: ENGLISH Document Type: ARTICLE
Abstract: It is well established that osteoclasts , the cells responsible for bone resorption, are derived from hematopoietic progenitors (CFU-GM), whereas the bone -forming osteoblasts are of the same lineage as the mesenchymal stromal cells of the bone marrow. Moreover, it is widely accepted that osteoclast formation depends on cells of the stromal/osteoblastic lineage. The appreciation of the ontogeny of osteoclasts and osteoblasts , the interaction between them, and the role of local factors that regulate their development has led to the emergence of new insights into the pathophysiology of the osteopenias associated with estrogen deficiency and senescence. Consistent with histomorphometric data from humans, there is now evidence from studies in animal models suggesting that a critical cellular change caused by the loss of ovarian, as well as testicular, function is an increase in osteoclastogenesis . This change is apparently mediated by an increase in the production of the osteoclastogenic cytokine interleukin-6 by cells of the bone marrow, which follows the removal of an inhibiting control of estrogens or androgens on IL-6. The inhibiting effect of sex steroids on IL-6 production is mediated by their respective receptors and is exerted indirectly on the transcriptional. activity of the proximal 225 bp sequence of the IL-6 gene promoter. Besides its effects on IL-6 production, loss of gonadal function may also cause an increase in the sensitivity of the osteoclastic precursors to the action of cytokines such as IL-6, due to an upregulation of the gp 130 signal transduction pathway. The osteopenia associated with aging, however, appears to be due to a decrease in the ability of the bone marrow to form osteoblastic cells, as evidenced by a decrease in the number of colony forming units-fibroblasts (CFU-F), the progenitor of the stromal/osteoblastic cell lineage, end the number of colonies exhibiting mineralization, termed colony forming units-osteoblasts (CFU-OB), in murine models of senescence.

4/AB/29 (Item 21 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03894636 Genuine Article#: QN329 Number of References: 87
Title: DIAGNOSIS AND THERAPY OF MULTIPLE-MYELOMA - NEW ASPECTS (Abstract Available)
Author(s): BETTICHER DC; CERNY T; FEY MF
Corporate Source: CHRISTIE HOSP,DEPT MED ONCOL,WILMSLOW RD/MANCHESTER M20 4BX/LANCS/ENGLAND/; INSELSPITAL BERN,INST MED ONKOL/BERN//SWITZERLAND/
Journal: SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT, 1995, V125, N11 (MAR 18), P541-551
ISSN: 0036-7672
Language: GERMAN Document Type: ARTICLE
Abstract: The crucial first step in management of multiple myeloma is to be certain regarding the diagnosis. Multiple myeloma must be distinguished from monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma. Therapy should be administered to patients with advanced and active myeloma involving anemia, osteolysis or

renal failure. Chemotherapy with a single agent (melphalan) is the preferred initial treatment for overt, symptomatic multiple myeloma. Cytostatic drug combinations produce a higher response rate, but survival and remission duration are the same compared with melphalan/prednisone therapy. However, in patients with renal failure and/or poor prognostic factors (advanced stage, elevated beta(2)-microglobulin, high bone marrow plasma cell labeling index, high levels of C-reactive protein and lactate dehydrogenase and/or nodular pattern of bone marrow infiltration), combined treatment with adriamycin, vincristine and prednisone should be administered to prevent nephrotoxicity and attain a rapid paraprotein decrease. Alpha interferon treatment as maintenance seems to prolong the duration of the plateau state after response to chemotherapy, but apparently does not prolong survival. Allogeneic bone marrow transplantation involves significant early mortality (50%); the risk of graft versus host disease, infections and renal failure is a problem, and relapse is common. High dose chemotherapy followed by autologous bone marrow transplantation or peripheral blood stem cell reinfusion may prolong survival and free time to progression, but, to date, there are no indications of cure. This therapeutic procedure, therefore, should be considered for randomized trials for young patients with poor prognostic factors.

4/AB/30 (Item 22 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03794823 Genuine Article#: QF985 Number of References: 61
Title: MECHANISMS BY WHICH CELLS OF THE OSTEOBLAST LINEAGE CONTROL OSTEOCLAST FORMATION AND ACTIVITY (Abstract Available)
Author(s): MARTIN TJ; NG KW
Corporate Source: UNIV MELBOURNE,ST VINCENTS HOSP,ST VINCENTS INST MED RES,DEPT MED,41 VICTORIA PARADE/MELBOURNE/VIC 3065/AUSTRALIA/
Journal: JOURNAL OF CELLULAR BIOCHEMISTRY, 1994, V56, N3 (NOV), P357-366
ISSN: 0730-2312
Language: ENGLISH Document Type: ARTICLE
Abstract: The cells of bone are of two lineages, the osteoblasts arising from pluri potential mesenchymal cells and osteoclasts from hemopoietic precursors of the monocyte-macrophage series. Resorption of bone by the multinucleate osteoclast requires the generation of new osteoclasts and their activation. Many hormones and cytokines are able to promote bone resorption by influencing these processes, but they achieve this without acting directly on osteoclasts . Most evidence indicates that their actions are mediated by cells of the osteoblast lineage. Evidence for hormone- and cytokine-induced activation of osteoclasts requiring the mediation of osteoblasts comes from studies of resorption by isolated osteoclasts . However, consistent evidence for a specific ''activating factor'' is lacking, and the argument is presented that the isolated osteoclast resorption assays have not been shown convincingly to be assays of osteoclast activation. The view is presented that osteoblast -mediated osteoclast activation is the result of several events in the microenvironment without necessarily requiring the existence of a specific, essential osteoclast activator. On the other hand, a specific promoter of osteoclast differentiation does seem likely to be a product of cells of the stromal/osteoblast series. Evidence in favour of this comes from studies of osteoclast generation in co-cultures of osteoblast /stromal cells with hemopoietic cells. Conflicting views, maintaining that osteoclasts can develop from hemopoietic cells without stromal intervention, might be explained by

varying criteria used in identification of osteoclasts . Osteoblastic and osteoclastic renewal, and the interactions of these lineages, are central to the process of bone remodeling. (C) 1994 Wiley-Liss, Inc.

4/AB/31 (Item 23 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03771027 Genuine Article#: QD586 Number of References: 53
Title: CYTOKINE AND HORMONAL-STIMULATION OF HUMAN OSTEOSARCOMA INTERLEUKIN- 11 PRODUCTION (Abstract Available)
Author(s): ELIAS JA; TANG WL; HOROWITZ MC
Corporate Source: YALE UNIV,SCH MED,DEPT INTERNAL MED,PULM CRIT CARE MED SECT,333 CEDAR ST,1105 LCI/NEW HAVEN//CT/06250; YALE UNIV,SCH MED,DEPT ORTHOPED & REHABIL/NEW HAVEN//CT/06250; VET ADM MED CTR,RES SERV/W HAVEN//CT/06516
Journal: ENDOCRINOLOGY, 1995, V136, N2 (FEB), P489-498
ISSN: 0013-7227
Language: ENGLISH Document Type: ARTICLE
Abstract: Osteoclast -mediated bone resorption plays a crucial role in osseous remodeling. Osteoblasts are important regulators of this activity, in part through their ability to produce osteoclast -regulating soluble factors such as interleukin-6 (IL-6). IL -11 is a newly appreciated pleotropic cytokine whose spectrum of biological activities overlaps with that of IL-6. As a result, we hypothesized that osteoblasts are an important skeletal source of this cytokine. To test this hypothesis, we characterized the IL -11 production of unstimulated and stimulated SaOS-2 human osteosarcoma cells. Unstimulated cells produced modest amounts of IL -11 . The osteotropic agents recombinant IL-1 (0.25-5 ng/ml), transforming growth factor-beta 1 (0.1-10 ng/ml), PTH (10(-8)-10(-11) M), and PTH-related peptide (10(-8)-10(-11) M) further increased SaOS-2 cell IL -11 protein production and messenger RNA accumulation. These stimulatory effects were dose and time dependent, and the IL -11 that was produced was bioactive, as demonstrated by its ability to stimulate the proliferation of T10D plasmacytoma cells. The protein kinase-C activator, 12-O-Tetra-decanoylphorbol 13-acetate, and a variety of cAMP agonists [forskolin, prostaglandin E(1), prostaglandin E(2), and (Bu)(2)AMP] also stimulated osteoblast IL -11 protein production and messenger RNA accumulation. In contrast, recombinant IL-4, recombinant interferon-gamma, and endotoxin did not stimulate SaOS-2 cells in a similar fashion. Importantly, the ability to produce IL -11 was not a unique property of SaOS-2 cells, because primary human trabecular bone osteoblasts also produced significant amounts of bioactive IL -11 when stimulated with transforming growth factor-beta 1. These studies demonstrate that appropriately stimulated human osteoblasts and osteoblast -like cells are potent producers of IL -11 and suggest that osteoblast -derived IL -11 may be an important component of the cytokine network mediating osteoblast - osteoclast communication in normal and pathological bone remodeling.

4/AB/32 (Item 24 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

03689834 Genuine Article#: PY200 Number of References: 71
Title: IMPLICATIONS OF THE POLYFUNCTIONALITY OF HEMATOPOIETIC REGULATORS (Abstract Available)

Author(s): METCALF D
Corporate Source: ROYAL MELBOURNE HOSP,WALTER & ELIZA HALL INST MED RES,PO ROYAL MELBOURNE HOSP/MELBOURNE/VIC 3050/AUSTRALIA/
Journal: STEM CELLS, 1994, V12, S1, P259-275
ISSN: 1066-5099
Language: ENGLISH Document Type: ARTICLE
Abstract: Studies on the expanding group of hemopoietic regulators have identified several types of situations indicating the polyfunctionality of these regulators. In actions on hemopoietic populations, this polyfunctionality is seen in cross-lineage actions, in proliferative actions on cells at multiple stages within a lineage and, above all, in actions that do not simply control cell proliferation but also aspects of differentiation commitment, maturation and the functional activity of mature cells.

More perplexing are the growing lists of actions on non-hemopoietic tissues, seen in extreme form with the leukemia inhibitory factor group of regulators. The bizarre range of actions exhibited by regulators of this group is difficult to explain but may be indicating the unsuspected existence of some novel integrated bioorgan systems.

4/AB/33 (Item 25 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2001 Inst for Sci Info. All rts. reserv.

01748701 Genuine Article#: HX974 Number of References: 46
Title: HUMAN INTRAOVARIAN INTERLEUKIN-1 (IL-1) SYSTEM - HIGHLY COMPARTMENTALIZED AND HORMONALLY DEPENDENT REGULATION OF THE GENES ENCODING IL-1, ITS RECEPTOR, AND ITS RECEPTOR ANTAGONIST (Abstract Available)
Author(s): HURWITZ A; LOUKIDES J; RICCIARELLI E; BOTERO L; KATZ E; MCALLISTER JM; GARCIA JE; ROHAN R; ADASHI EY; HERNANDEZ ER
Corporate Source: UNIV MARYLAND,SCH MED,DEPT OBSTET & GYNECOL,DIVREPROD ENDOCRINOL,655 W BALTIMORE ST,11TH FLOOR/BALTIMORE//MD/21201; UNIV MARYLAND,SCH MED,DEPT OBSTET & GYNECOL,DIVREPROD ENDOCRINOL,655 W BALTIMORE ST,11TH FLOOR/BALTIMORE//MD/21201; UNIV MARYLAND,SCH MED,DEPT PHYSIOL/BALTIMORE//MD/21201; UNIV TEXAS,SW MED CTR,DEPT OBSTET GYNECOL & BIOCHEM/DALLAS//TX/75080; GREATER BALTIMORE MED CTR,DIV REPROD ENDOCRINOL/BALTIMORE//MD/21204
Journal: JOURNAL OF CLINICAL INVESTIGATION, 1992, V89, N6 (JUN), P1746-1754
Language: ENGLISH Document Type: ARTICLE
Abstract: To delineate the scope of the human intraovarian IL-1 system we used a solution hybridization/RNase protection assay to test for expression of the genes encoding IL-1, its type I receptor (IL-1R), and its receptor antagonist (IL-1RA). IL-1 transcripts were not detected in whole ovarian material from days 4 or 12 of an unstimulated menstrual cycle but transcripts (IL-1-beta >> IL -11 -alpha) were detected in preovulatory follicular aspirates from gonadotropin-stimulated cycles. Concurrently obtained peripheral monocytes did not contain IL-1-beta transcripts but macrophage-depleted follicular aspirates did, thus implicating the granulosa cells as the site of IL-1 expression. IL-1R transcripts were detected in RNA from whole ovaries and follicular aspirates but not in RNA from peripheral monocytes. IL-1RA transcripts were detected in whole ovarian material as well as in macrophage-free follicular aspirates. Cultured human granulosa and theca cells did not contain mRNA for IL-1-beta or IL-1RA but did contain mRNA for IL-1R. Treatment of cell cultures with forskolin (25-mu-M) induced IL-1-beta transcripts in granulosa but not theca cells. Forskolin also increased the basal levels of IL-1R transcripts in both granulosa and theca cells but did not induce IL-RA transcripts in either cell type. Taken

together, these findings reveal the existence of a complete, highly compartmentalized, hormonally dependent intraovarian IL-1 system replete with ligands, receptor, and receptor antagonist.

4/AB/34 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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07720861 EMBASE No: 1999197199
Local estrogen biosynthesis in males and females
Simpson E.; Rubin G.; Clyne C.; Robertson K.; O'Donnell L.; Davis S.; Jones M.
E. Simpson, Prince Henry's Inst. of Medical Res., PO Box 5152, Clayton, Vic. 3168 Australia
Endocrine-Related Cancer (ENDOCR.-RELAT. CANCER) (United Kingdom) 1999, 6/2 (131-137)
CODEN: ERCAE ISSN: 1351-0088
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 43

It is now apparent that in men and in postmenopausal women, estrogens have important physiological and pathophysiological roles. However, importantly, these actions are at a ocal level, namely paracrine, autocrine, and even 'intracrine' rather than endocrine in the classical sense. Thus for example local estrogen biosynthesis in the bones of men plays a hitherto unsuspected role in the maintenance of bone mineralization and in epiphyseal fusion; and in the testes, estrogen is essential for male germ cell development. On the other hand, in postmenopausal women, the mesenchymal cells of the breast are the major source of estrogen responsible for breast cancer development. This realization points to the importance of circulating Cinf 1inf 9 precursors in the maintenance of adequate estrogen biosynthesis in extragonadal sites and suggests the possibility of new therapies to block estrogen synthesis in a tissue-specific fashion.

4/AB/35 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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07544428 EMBASE No: 1999019517
Bone and cytokines: Beyond IL-1, IL-6 and TNF-alpha
Rifas L.
L. Rifas, Department of Internal Medicine, Division of Bone/Mineral Diseases, Washington Univ. School of Medicine, St. Louis, MO United States
Calcified Tissue International (CALCIF. TISSUE INT.) (United States) 1999, 64/1 (1-7)
CODEN: CTIND ISSN: 0171-967X
DOCUMENT TYPE: Journal; Editorial
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 106

4/AB/36 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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07153070 EMBASE No: 1998041873

Leukemia inhibitory factor in human reproduction
Senturk L.M.; Arici A.
A. Arici, Dept. of Obstetrics and Gynecology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520-8053 United States
American Journal of Reproductive Immunology (AM. J. REPROD. IMMUNOL.) (Denmark) 1998, 39/2 (144-151)
CODEN: AAJID ISSN: 8755-8920
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 94

PROBLEM: Leukemia inhibitory factor (LIF) is a pleiotropic cytokine of the interleukin-6 family and has different biological actions in various tissue systems. Although named for its ability to inhibit proliferation of a myeloid leukemic cell line by inducing differentiation, it also regulates the growth and differentiation of embryonic stem cells, primordial germ cells, peripheral neurons, osteoblasts , adipocytes, and endothelial cells. LIF is crucial for successful implantation of the embryo in mice. Currently, there is an accumulation of data about the role of LIF in human reproduction. METHOD OF STUDY: This review of the literature and of our studies focuses on the expression, regulation, and effects of LIF in the human endometrium, fallopian tube, and ovarian follicle. RESULTS: Human endometrium expresses LIF in a menstrual cycle-dependent manner. Maximal expression is observed between days 19 and 25 of the menstrual cycle, coinciding with the time of implantation. Various cytokines and growth factors induce endometrial LIF expression in vitro. LIF receptor is expressed in endometrial tissue throughout the menstrual cycle and on human blastocysts in a stage-dependent manner. Affecting the trophoblast differentiation pathway toward the adhesive phenotype, LIF plays a role in implantation. LIF is also expressed and secreted by the epithelial cells of the fallopian tube. Its increased expression in the tubal stromal cell cultures by the inflammatory cytokines suggests a link between salpingitis and ectopic implantation in the tube. The rising follicular fluid LIF level around the time of ovulation indicates that LIF may play a role in ovulatory events, early embryonic development, and implantation. CONCLUSIONS: There is growing evidence that LIF may be one of the entities that plays a role in human reproduction.

4/AB/37 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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07108133 EMBASE No: 1997369257
Estrogen biosynthesis in THP1 cells is regulated by promoter switching of the aromatase (CYP19) gene
Shozu M.; Zhao Y.; Simpson E.R.
Dr. E.R. Simpson, GCRBS, DOGB, UTSMC, 5323 Harry Hines Boulevard, Dallas, TX 75235-9051 United States
AUTHOR EMAIL: simpson@grnctr.swmed.edu
Endocrinology (ENDOCRINOLOGY) (United States) 1997, 138/12 (5125-5135)
CODEN: ENDOA ISSN: 0013-7227
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 42

The expression of aromatase, the enzyme responsible for estrogen biosynthesis, has been studied in THP-1 cells of human mononuclear leukemic origin, which exhibit high rates of aromatase activity. These cells have the capacity to differentiate in the presence of vitamin D into cells with osteoclast -like properties. Differentiated cells displayed higher rates of

aromatase than undifferentiated cells, and, in both cases, activity was stimulated 10- to 20-fold by dexamethasone. Phorbol esters also increased aromatase activity, but the effect was the same in differentiated as in undifferentiated cells. In a similar fashion to adipose stromal cells, serum potentiated the response to dexamethasone but had no effect on phorbol ester- stimulated activity. By contrast to its action in adipose stromal cells, (Bu)inf 2cAMP markedly inhibited aromatase activity of THP-1 cells, as did factors whose actions are mediated by cAMP, such as PTH and PTH-related peptide. This was true of control cells, as well as of dexamethasone- and phorbol ester-stimulated cells. Previously we have shown that type 1 cytokines as well as tumor necrosis factor-a stimulate aromatase activity of adipose stromal cells in the presence of dexamethasone. By contrast, interleukin-6, interleukin -11 , and leukemia-inhibitory factor had no effect on aromatase activity of THP-1 cells, whereas tumor necrosis factor-alpha, oncostatin M, and platelet-derived growth factor were slightly inhibitory of aromatase activity. Exon-specific Southern analysis of rapid amplification of cDNA ends-amplified transcripts was employed to examine the distribution of the various 5'-termini of aromatase transcripts. In the control group, most of the clones contained transcripts specific for the proximal promoter II, whereas in dexamethasone-treated cells, most transcripts contained exon I.4. In the phorbol ester-treated cells, a broader spectrum of transcripts was present, with equal proportions of I.4, II, and I.3-containing clones. Additionally, one clone containing a new sequence, exon I.6, was found. This was shown to be located about 1 kb upstream of exon II. By contrast, all clones from cells treated with (Bu)inf 2cAMP contained promoter II-specific sequences. In addition to these transcripts, two clones in the library from the dexamethasone-treated cells contained the sequence previously defined as the brain-specific sequence, 1f. In one of these the if sequence was fused downstream of exon I.4. indicative that its expression likely employed promoter I.4. These results point to similarities and important differences between aromatase expression in THP-1 cells and other cells such as adipose stromal cells, indicative of unique regulatory pathways governing aromatase expression in these cells.

4/AB/38 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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06407787 EMBASE No: 1996058306
The role of cytokines and growth factors as mediators of the effects of systemic hormones at the bone local level
Riancho J.A.; Mundy G.R.
Department of Internal Medicine, University of Cantabria, Hospital M. Valdecilla,Santander 39008 Spain
Critical Reviews in Eukaryotic Gene Expression (CRIT. REV. EUKARYOTIC GENE EXPR.) (United States) 1995, 5/3-4 (193-217)
CODEN: CRGEE ISSN: 1045-4403
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Bone tissue is being continuously remodeled by the integrated activity of bone -resorbing osteoclasts and bone forming osteoblasts . Because bone remodeling takes place in discrete foci throughout the skeleton, local mechanisms must play a critical role in its regulation. Several cytokines and other locally released factors exert marked effects on bone cells. Many experimental studies show that calciotropic hormones modulate cytokine expression. Indeed, a number of studies suggest that cytokines are actually involved in the mechanisms that mediate the effects of calciotropic hormones at the areas of bone being remodeled. However, the

results are often conflicting. Moreover, most published studies have been carried out by testing the effects of pharmacological concentrations of hormones on cytokine production by bone cells. This type of study often gives little information on the physiological role of the factors tested. Thus, although evidence for a role of cytokines as mediators of hormone effects at the bone local level is rapidly accumulating, more data are needed in order to better understand the actual role of those factors in bone physiology and pathophysiology. In vivo studies and particularly those analyzing the consequences of the lack of activity of a particular cytokine or hormone are likely to be particularly informative.

4/AB/39 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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06012536 EMBASE No: 1995041338
Mechanisms of disease: Bone marrow, cytokines, and bone remodeling - Emerging insights into the pathophysiology of osteoporosis
Manolagas S.C.; Jilka R.L.
Arkansas Univ. for Medical Sciences, 4301 W. Markham,Little Rock, AR 72205 United States
New England Journal of Medicine (NEW ENGL. J. MED.) (United States)
1995, 332/5 (305-311)
CODEN: NEJMA ISSN: 0028-4793
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Both osteoblasts and osteoclasts are derived from progenitors that reside in the hone marrow; osteoblasts belong to the mesenchymal lineage of the marrow stroma, and osteoclasts to the hematopoietic lineage. The development of osteoclasts from their progenitors is dependent on stromal-osteoblastic cells, which are a major source of cytokines that are critical in osteoclastogenesis , such as interleukin-6 and interleukin -11 . The production of interleukin-6 by stromal-osteoblastic cells, as well as the responsiveness of hone marrow cells to cytokines such as interleukin-6 and interleukin -11 , is regulated by sex steroids. When gonadal function is lost, the formation of osteoclasts as well as osteoblasts increases in the marrow, both changes apparently mediated by an increase in the production of interleukin-6 and perhaps by an increase in the responsiveness of bone marrow progenitor cells not only to interleukin-6 but also to other cytokines with osteoclastogenic and osteoblastogenic properties. The cellular activity of the hone marrow is also altered by the process of aging. Specifically, senescence may decrease the ability of the marrow to form osteoblast precursors. The association between the dysregulation of osteoclast or osteoblast development in the marrow and the disruption of the balance between bone resorption and bone formation, resulting in the loss of bone , leads to the following notion. Like homeostasis of other regenerating tissues, homeostasis of bone depends on the orderly replenishment of its cellular constituents. Excessive osteoclastogenesis and inadequate osteoblastogenesis are responsible for the mismatch between the formation and resorption of bone in postmenopausal and age-related osteopenia . The recognition that changes in the numbers of bone cells, rather than changes in the activity of individual cells, form the pathogenetic basis of osteoporosis is a major advance in understanding the mechanism of this disease.

4/AB/40 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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05989991 EMBASE No: 1995018602
Rational design of a receptor super-antagonist of human interleukin-6
Savino R.; Ciapponi L.; Lahm A.; Demartis A.; Cabibbo A.; Toniatti C.; Delmastro P.; Altamura S.; Ciliberto G.
Department of Genetics, Ist Ricerche Biologia Molecolare, Via Pontina km 30 600,00040 Pomezia Italy
EMBO Journal (EMBO J.) (United Kingdom) 1994, 13/24 (5863-5870)
CODEN: EMJOD ISSN: 0261-4189
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Interleukin-6 (IL-6) is a differentiation and growth factor for a variety of cell types and its excessive production plays a major role in the pathogenesis of multiple myeloma and post-menopausal osteoporosis . IL-6, a four-helix bundle cytokine, is believed to interact sequentially with two transmembrane receptors, the low-affinity IL-6 receptor (IL-6Ralpha) and the signal transducer gp130, via distinct binding sites. In this paper we show that combined mutations in the predicted A and C helices, previously suggested to establish contacts with gp130, give rise to variants with no bioactivity but unimpaired binding to IL-6Ralpha. These mutants behave as full and selective IL-6 receptor antagonists on a variety of human cell lines. Furthermore, a bifacial mutant was generated (called IL-6 super-antagonist) in which the antagonist mutations were combined with amino acid substitutions in the predicted D helix that increase binding for IL-6Ralpha. The IL-6 super-antagonist has no bioactivity, but improved first receptor occupancy and, therefore, fully inhibits the wild-type cytokine at low dosage. The demonstration of functionally independent receptor binding sites on IL-6 suggests that it could be possible to design super-antagonists of other helical cytokines which drive the assembly of structurally related multisubunit receptor complexes.

4/AB/41 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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05283343 EMBASE No: 1993051428
Interleukin-6: A cytokine for gerontologists
Ershler W.B.
U.W. Institute on Aging, 425 Henry Mall,Madison, WI 53706 United States
Journal of the American Geriatrics Society (J. AM. GERIATR. SOC.) (United States) 1993, 41/2 (176-181)
CODEN: JAGSA ISSN: 0002-8614
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Interleukin-6 (IL-6) is a multifunctional cytokine that presumably plays its major role as a mediator of several of the acute phase inflammatory responses. These include inflammatory cell and lymphocyte activation and hepatocellular stimulation of acute phase protein synthesis. IL-6 expression is normally low, and serum levels are usually non-detectable in the absence of inflammation. However, with advancing age, serum levels become detectable, and it is proposed that this reflects an age-associated loss in the normal regulation of gene expression for this molecule. The cause of this is most likely multi-factorial, but there is evidence that it relates to an age- associated loss of T cell immunoregulatory functions as well as menopausal loss of estrogen. In any event, the 'inappropriate' presence of IL-6 results in many changes typical of chronic inflammation. There is also speculation that IL-6 may contribute to the pathogenesis of several diseases of late- life including lymphoma, osteoporosis , and

Alzheimer's disease. In this review the biology of this important cytokine is presented and its relevance to gerontology is highlighted.

4/AB/42 (Item 1 from file: 94)
DIALOG(R)File 94:JICST-EPlus
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04165780 JICST ACCESSION NUMBER: 99A0493009 FILE SEGMENT: JICST-E
The elucidation of crisis mechanism of postmenopausal osteoporosis which noticed bone-marrow hemopoiesis regulatory effect of the estrogen. (Ministry of Health and Welfare S).
MIYAURA CHISATO (1)
(1) Showa Univ., Sch. of Dent.
Choju Kagaku Sogo Kenkyu, 1998, VOL.1997(4), PAGE.363-367, REF.9
JOURNAL NUMBER: J1099AAA
UNIVERSAL DECIMAL CLASSIFICATION: 616.7-09 591.177.05+591.471 577.175.6
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Original paper
MEDIA TYPE: Printed Publication

4/AB/43 (Item 2 from file: 94)
DIALOG(R)File 94:JICST-EPlus
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03444834 JICST ACCESSION NUMBER: 98A0075691 FILE SEGMENT: JICST-E
Levels of Interleukin-6 and Soluble Interleukin-6 Receptors After Surgical Menopause: Effects on Bone Metabolism.
MUSHA CHIEKO (1)
(1) Tokyo Women's Med. Coll.
Tokyo Joshi Ika Daigaku Zasshi(Journal of Tokyo Women's Medical College), 1997, VOL.67,NO.11, PAGE.919-927, FIG.5, TBL.3, REF.42
JOURNAL NUMBER: G0684AAY ISSN NO: 0040-9022 CODEN: TJIZA
UNIVERSAL DECIMAL CLASSIFICATION: 616.431/.438 616.7
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Original paper
MEDIA TYPE: Printed Publication
ABSTRACT: Interleukin-6(IL-6) has been postulated to play a role in the pathogenesis of postmenopausal osteoporosis . The study included 46 premenopausal women; 30 healthy women underwent abdominal surgery without bilateral oophorectomy and 16 healthy women underwent total hysterectomy with bilateral oophorectomy. To test this hypothesis, we measured circulating levels of IL-6, soluble interleukin-6 receptors(IL-6sR) and other bone biochemical markers; tartrate-resistant acid phosphatase (TRACP), intact osteocalcin (I-OC), bone alkaline phosphatase (B-ALP) and urinary deoxypyridinoline (D-Pyr) corrected for urinary concentration according to individual creatinine values. Laboratory parameters were tested before surgery and 1 month, 3 months and 6 months after surgery in all patients. Additionally bone mineral density (BMD; L2-L4) was tested before surgery and at 6 months. A significant increase in the levels of serum IL-6sR, TRACP at 3 months and in serum B-ALP and I-OC and urine D-Pyr at 6 months were reported. BMD decreased by 5.6% at 6 months. IL-6sR correlated with TRACP at 3 months after surgery. No significant variation was observed in the women without bilateral oophorectomy at any period of the study. These results confirm that IL-6sR play an important role in regulating bone resorption in postmenopausal osteoporosis . (author abst.)

4/AB/44 (Item 3 from file: 94)
DIALOG(R)File 94:JICST-EPlus
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02657373 JICST ACCESSION NUMBER: 95A0754331 FILE SEGMENT: JICST-E
Changes on serum interleukin 6 and soluble interleukin 6 receptors in the perimenopausal stage.
MARUO NAOKO (1); CHIN ZUITO (2); OGATA ETSURO (2); KAMI KATSUHIKO (3); SHIRAKI MASATAKA (3); MORITA IKUO (4)
(1) Tosoh Corp.; (2) Cancer Inst. Hosp., Jpn. Found. for Cancer Res.; (3) Seijinbyoshinryoken; (4)Tokyo Medical and Dental Univ., Graduate School
Nippon Kotsu Taisha Gakkai Zasshi(Journal of Bone and Mineral Metabolism), 1995, VOL.13,NO.2, PAGE.130
JOURNAL NUMBER: X0157AAW ISSN NO: 0910-0067
UNIVERSAL DECIMAL CLASSIFICATION: 616.7-071
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Short Communication
MEDIA TYPE: Printed Publication

4/AB/45 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
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12320885 PASCAL No.: 95-0559919
L'os apres la menopause : Gynecologie : l'apres- menopause : les perspectives actuelles de consensus
(Bone after menopause)
PERETZ A
Hop. univ. Brugmann, clin. rhumatologie, dep. medecine, Bruxelles, Belgium
Journal: Revue medicale de Bruxelles, 1995, 16 (4) 280-284
Language: French Summary Language: English
L'os est un tissu qui subit un constant remodelage sous l'influence d'hormones et de facteurs locaux ou paracrines. Apres avoir atteint un pic, la masse osseuse diminue avec l'age tout en presentant une acceleration de ce phenomene dans les annees qui suivent la menopause . Le remodelage est compose d'une phase de resorption osseuse mediee par les osteoclastes etroitement couplee a une phase de formation osseuse qui est l'oeuvre des osteoblastes . Les osteoclastes et les osteoblastes sont tous deux issus de la moelle osseuse et partagent avec les cellules de la lignee hematopoietique des proprietes communes. Les deux lignees synthetisent et repondent a des cytokines telles que l'interleukine 1, l'interleukine 6 et l' interleukine 11 ou a des facteurs de croissance comme les colony stimulating factors (CSF). Les mecanismes qui regulent l'activation des osteoclastes et des osteoblastes en situation physiologique ou au cours de la carence hormonale sont de mieux en mieux connus, ce qui permetrait dans un avenir proche de proposer une therapeutique plus efficace peut-etre, plus rationnelle certainement.

4/AB/46 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI
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012890543
WPI Acc No: 2000-062377/200005
XRAM Acc No: C00-017289

Inhibiting formation of a tertiary complex for the treatment of osteoporosis
Patent Assignee: HAMILTON CIVIC HOSPITAL RES DEV CORP (HAMI-N); AUSTIN R C (AUST-I); SHAUGHNESSY S (SHAU-I)
Inventor: AUSTIN R C; SHAUGHNESSY S
Number of Countries: 085 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9959608	A2	19991125	WO 99CA516	A	19990519	200005	B
CA 2237915	A1	19991119	CA 2237915	A	19980519	200017	
AU 9940277	A	19991206	AU 9940277	A	19990519	200019	

Priority Applications (No Type Date): CA 2237915 A 19980519
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9959608	A2	E	61	A61K-038/00	

Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW

CA 2237915	A1	E	A61K-039/395	
AU 9940277	A		A61K-038/00	Based on patent WO 9959608

Abstract (Basic): WO 9959608 A2
Abstract (Basic):

NOVELTY - A method of treating or alleviating the symptoms of a pathological condition in which bone density is decreased comprises inhibiting the formation of a tertiary complex of interleukin -11 (IL -11), IL -11 receptor (IL -11R) and glycopeptide 130 (gp130) in a mammalian patient suffering from such a condition.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising a mutant IL -11R , an IL -11 or IL -11R binding peptide; and

(2) a composition useful in inhibiting IL -11 /IL -11R or IL -11R /gp130 interactions comprising an antibody which specifically binds the IL -11R and blocks interactions between IL -11 and IL -11R or between IL -11R and gp130.

ACTIVITY - Osteoporotic .

MECHANISM OF ACTION - IL -11 Antagonist.

USE - The method is used to treat or alleviate the symptoms of a pathological condition in which bone density is decreased, especially postmenopausal bone loss. The IL -11 binding peptide is useful in the purification of IL -11 or in depleting IL -11 from a solution. (All claimed). The use of TRAP (tartrate-resistant acid phosphatase) and bone marrow formation assays for the identification of IL -11 antagonists are also claimed.

ADVANTAGE - The method not only inhibits bone resorption and hence bone loss, but also increases the process of bone formation to increase bone density.

pp; 61 DwgNo 0/0

?ds

Set	Items	Description
S1	11415	(IL OR INTERLEUKIN?)(W)11 OR (IL OR INTERLEUKIN?)(W)(11R OR 11(W)R OR RECEPTOR) OR (GP OR GLYCOPROTEIN?)(W)130
S2	2932	S1 AND (OSTEO? OR OSTEOPOROS? OR BONE? OR BONY)
S3	81	S2 AND (MENSTRUAL? OR POSTMENOPAUS? OR MENOPAUS?)
S4	46	RD (unique items)

S5 1 S4 AND TERTIARY
?t s5/3 ab/1

5/AB/1 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI
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012890543
WPI Acc No: 2000-062377/200005
XRAM Acc No: C00-017289
Inhibiting formation of a tertiary complex for the treatment of osteoporosis
Patent Assignee: HAMILTON CIVIC HOSPITAL RES DEV CORP (HAMI-N); AUSTIN R C (AUST-I); SHAUGHNESSY S (SHAU-I)
Inventor: AUSTIN R C; SHAUGHNESSY S
Number of Countries: 085 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9959608	A2	19991125	WO 99CA516	A	19990519	200005	B
CA 2237915	A1	19991119	CA 2237915	A	19980519	200017	
AU 9940277	A	19991206	AU 9940277	A	19990519	200019	

Priority Applications (No Type Date): CA 2237915 A 19980519
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9959608	A2	E	61	A61K-038/00	
CA 2237915	A1	E		A61K-039/395	
AU 9940277	A			A61K-038/00	Based on patent WO 9959608

Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW

Abstract (Basic): WO 9959608 A2
Abstract (Basic):

NOVELTY - A method of treating or alleviating the symptoms of a pathological condition in which bone density is decreased comprises inhibiting the formation of a tertiary complex of interleukin -11 (IL -11), IL -11 receptor (IL -11R) and glycopeptide 130 (gp130) in a mammalian patient suffering from such a condition.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a composition comprising a mutant IL -11R , an IL -11 or IL -11R binding peptide; and

(2) a composition useful in inhibiting IL -11 /IL -11R or IL -11R /gp130 interactions comprising an antibody which specifically binds the IL -11R and blocks interactions between IL -11 and IL -11R or between IL -11R and gp130.

ACTIVITY - Osteoporotic .

MECHANISM OF ACTION - IL -11 Antagonist.

USE - The method is used to treat or alleviate the symptoms of a pathological condition in which bone density is decreased, especially postmenopausal bone loss. The IL -11 binding peptide is useful in the purification of IL -11 or in depleting IL -11 from a solution. (All claimed). The use of TRAP (tartrate-resistant acid phosphatase) and bone marrow formation assays for the identification of IL -11 antagonists are also claimed.

ADVANTAGE - The method not only inhibits bone resorption and hence bone loss, but also increases the process of bone formation

to increase bone density.
pp; 61 DwgNo 0/0
?

s IL-11 or interleukin-11
L1 4189 IL-11 OR INTERLEUKIN-11

=> s l1 (5a) antibod?
L2 76 L1 (5A) ANTIBOD?

=> s l2 (5a) (bone or osteo?)
L3 5 L2 (5A) (BONE OR OSTEO?)

=> d l3 1-5 bib ab

L3 ANSWER 1 OF 5 MEDLINE
AN 2000086480 MEDLINE
DN 20086480 PubMed ID: 10620068
TI Fluid shear stress increases interleukin-11 expression in human osteoblast-like cells: its role in osteoclast induction.
AU Sakai K; Mohtai M; Shida J; Harimaya K; Benvenuti S; Brandi M L; Kukita T; Iwamoto Y
CS Department of Orthopaedic Surgery, Faculty of Medicine, Kyushu University, Fukuoka, Japan.
SO JOURNAL OF BONE AND MINERAL RESEARCH, (1999 Dec) 14 (12) 2089-98. Journal code: 8610640. ISSN: 0884-0431.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200001
ED Entered STN: 20000204
Last Updated on STN: 20000204
Entered Medline: 20000127
AB It is unclear how mechanical stress influences bone cells. Mechanical stress causes fluid shear stress (FSS) in the bone. Osteoblast lineage cells are thought to sense FSS and regulate bone remodeling. We therefore investigated the effects of FSS on human osteoblast-like osteosarcoma cells: SaOS-2 cells in vitro. The conditioned medium of the SaOS-2 cells after 24 h of FSS (24 h-FSS CM) showed such osteoclastic phenotype inductions as significantly increasing the number of tartrate-resistant acid phosphatase (TRAP) positive multinuclear cells in rat bone marrow cells and TRAP-positive cells in human preosteoclastic cells: FLG 29.1 cells. An enzyme-linked immunosorbent assay showed interleukin-11 (IL-11) protein to increase 7-fold in the 24 h-FSS CM. A Northern analysis showed that IL-11 mRNA increased 4-fold in the SaOS-2 cells after 6 h-FSS; however, no IL-6 mRNA expression was detected. Furthermore, the anti-human **IL-11 antibody** significantly neutralized the **osteoclastic** phenotype induction of the 24 h-FSS CM. The IL-11 mRNA up-regulation in SaOS-2 cells by the 6 h-FSS was not inhibited by the anti-human transforming growth factor-beta1 antibody, but it was significantly inhibited by indomethacin. An enzymeimmunoassay showed prostaglandin E2 to increase 7-fold in the 1 h-FSS CM. These findings thus suggest that FSS induces osteoblasts to produce IL-11 (mediated by prostaglandins) and thus stimulates bone remodeling.

L3 ANSWER 2 OF 5 MEDLINE
AN 94216495 MEDLINE
DN 94216495 PubMed ID: 8163655
TI Interleukin-11: a new cytokine critical for osteoclast development.
AU Girasole G; Passeri G; Jilka R L; Manolagas S C
CS Section of Endocrinology and Metabolism, Veterans Affairs Medical Center, Indianapolis, Indiana.
NC AR-41313 (NIAMS)
SO JOURNAL OF CLINICAL INVESTIGATION, (1994 Apr) 93 (4) 1516-24. Journal code: 7802877. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199405
ED Entered STN: 19940606
Last Updated on STN: 19940606
Entered Medline: 19940520
AB Stromal cells of the bone marrow control the development of osteoclasts through the production of cytokines capable of promoting the proliferation and differentiation of hematopoietic progenitors. Moreover, the deregulated production of the cytokine IL-6 in the bone marrow mediates an increase in osteoclastogenesis after estrogen loss. IL-6, however, does not influence osteoclastogenesis in the estrogen-replete state, suggesting that other cytokines might be responsible for osteoclast development under physiologic circumstances. We report here that IL-11, a newly discovered cytokine that is produced by marrow stromal cells, induced the formation of osteoclasts exhibiting an unusually high degree of ploidy in cocultures of murine bone marrow and calvarial cells. Osteoclasts formed in the presence of IL-11 were capable of bone resorption, as evidenced by the formation of resorption pits, as well as the release of 45Ca from prelabeled murine calvaria. Further, an **antibody** neutralizing **IL-11** suppressed **osteoclast** development induced by either 1,25-dihydroxyvitamin D3, parathyroid hormone, interleukin-1, or tumor necrosis factor; whereas inhibitors of IL-1 or TNF had no effect on IL-11-stimulated osteoclast formation. The effects of IL-11 on osteoclast development were blocked by indomethacin; more important, however, they were independent of the estrogen status of the marrow donors.

L3 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2000:47203 CAPLUS
DN 133:16125
TI Fluid shear stress increases interleukin-11 expression in human osteoblast-like cells: its role in osteoclast induction
AU Sakai, Kenji; Mohtai, Masaaki; Shida, Jun-Ichi; Harimaya, Katsumi; Benvenuti, Susanna; Brandi, Maria L.; Kukita, Toshio; Iwamoto, Yukihide
CS Department of Orthopaedic Surgery, Faculty of Medicine, Kyushu University, Fukuoka, Japan
SO Journal of Bone and Mineral Research (1999), 14(12), 2089-2098
CODEN: JBMREJ; ISSN: 0884-0431
PB Blackwell Science, Inc.
DT Journal
LA English
AB It is unclear how mech. stress influences bone cells. Mech. stress causes fluid shear stress (FSS) in the bone. Osteoblast lineage cells are thought to sense FSS and regulate bone remodeling. We therefore investigated the effects of FSS on human osteoblast-like osteosarcoma cells: SaOS-2 cells in vitro. The conditioned medium of the SaOS-2 cells after 24 h of FSS (24 h-FSS CM) showed such osteoclastic phenotype inductions as significantly increasing the no. of tartrate-resistant acid phosphatase (TRAP) pos. multinuclear cells in rat bone marrow cells and TRAP-pos. cells in human preosteoclastic cells: FLG 29.1 cells. An ELISA showed interleukin-11 (IL-11) protein to increase 7-fold in the 24 h-FSS CM. A Northern anal. showed that IL-11 mRNA increased 4-fold in the SaOS-2 cells after 6 h-FSS; however, no IL-6 mRNA expression was detected. Furthermore, the anti-human **IL-11 antibody** significantly neutralized the **osteoclastic** phenotype induction of the 24 h-FSS CM. The IL-11 mRNA up-regulation in SaOS-2 cells by the 6 h-FSS was not inhibited by the anti-human transforming growth factor-.beta.1 antibody, but it was significantly inhibited by indomethacin. An enzymeimmunoassay showed prostaglandin E2 to increase 7-fold in the 1 h-FSS CM. These findings thus suggest that FSS induces osteoblasts to produce IL-11 (mediated by prostaglandins) and thus stimulates bone remodeling.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1999:753092 CAPLUS
DN 132:2795
TI Antagonists of interleukin 11-mediated osteoporotic bone loss
IN Shaughnessy, Stephen; Austin, Richard Carl
PA Hamilton Civic Hospital Research Development Corporation, Can.
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9959608	A2	19991125	WO 1999-CA516	19990519
	WO 9959608	A3	20000406		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	CA 2328486	AA	19991125	CA 1999-2328486	19990519
	AU 9940277	A1	19991206	AU 1999-40277	19990519
	EP 1079847	A2	20010307	EP 1999-923352	19990519
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2002515444	T2	20020528	JP 2000-549272	19990519
PRAI	CA 1998-2237915	A	19980519		
	WO 1999-CA516	W	19990519		

AB The authors disclose that interleukin-11 is a potent inhibitor of bone nodule formation, promotes osteoclast formation in bone marrow cultures, and mediates bone d. loss in a mouse osteoporosis model. In one example of interleukin-11 antagonism, the authors disclose that sol. IL-11 receptor constructs, modified at the gp130 binding site, ameliorate the IL-11-assocd. bone d. loss. In a second example, peptides derived from the ligand interaction site of IL-11R are also shown to reverse the pathol. bone loss.

L3 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1994:267936 CAPLUS
DN 120:267936
TI Interleukin-11: a New Cytokine Critical for Osteoclast Development
AU Girasole, G.; Passeri, G.; Jilka, R. L.; Manolagas, S. C.
CS Sect. Endocrinol. Metab., Veterans Affairs Med. Cent., Indianapolis, IN, 46202, USA
SO Journal of Clinical Investigation (1994), 93(4), 1516-24
CODEN: JCINAO; ISSN: 0021-9738
DT Journal
LA English
AB Stromal cells of the bone marrow control the development of osteoclasts through the prodn. of cytokines capable of promoting the proliferation and differentiation of hematopoietic progenitors. Moreover, the deregulated prodn. of the cytokine IL-6 in the bone marrow mediates an increase in osteoclastogenesis after estrogen loss. IL-6, however, does not influence osteoclastogenesis in the estrogen-replete state, suggesting that other cytokines might be responsible for osteoclast development under physiol. circumstances. The authors report here that IL-11, a newly discovered cytokine that is produced by marrow stromal cells, induced the formation of osteoclasts exhibiting an unusually high degree of ploidy in cocultures

of murine bone marrow and calvarial cells. Osteoclasts formed in the presence of IL-11 were capable of bone resorption, as evidenced by the formation of resorption pits, as well as the release of 45Ca from prelabeled murine calvaria. Further, an **antibody** neutralizing **IL-11** suppressed **osteoclast** development induced by either 1,25-dihydroxyvitamin D3, parathyroid hormone, interleukin-1, or tumor necrosis factor; whereas inhibitors of IL-1 or TNF had no effect on IL-11-stimulated osteoclast formation. The effects of IL-11 on osteoclast development were blocked by indomethacin; more important, however, they were independent of the estrogen status of the marrow donors.

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